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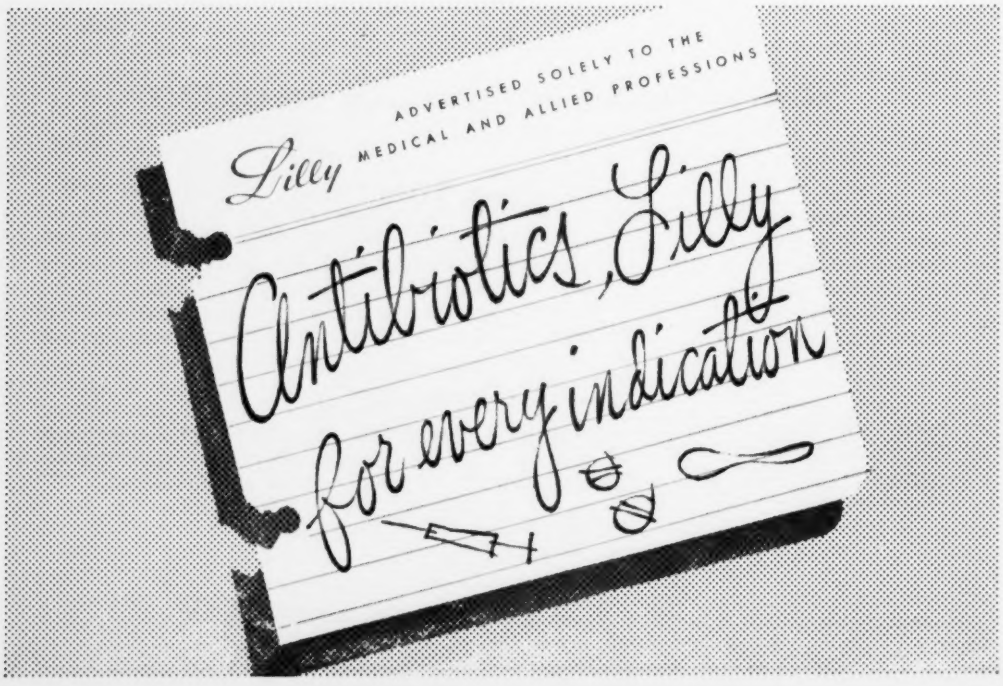

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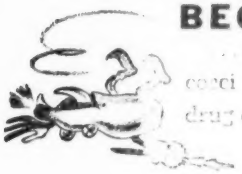

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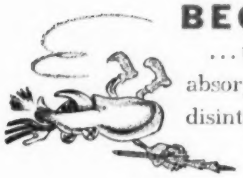

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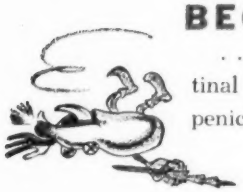

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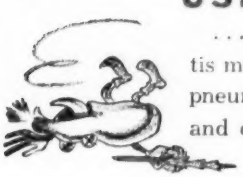

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Volume 249 AUGUST 27, 1953 Number 9

TOXOPLASMOSIS

Report of Two New Cases, with a Classification and with a Demonstration of the Organisms in the Human Placenta

RONALD S. BECKETT, M. D.,* AND FREDERICK J. FLYNN, JR., M.D.†

HARTFORD, CONNECTICUT

HUMAN toxoplasmosis is a disease of increasing importance. In this paper we shall review it briefly, report two new cases, suggest a classification of toxoplasmosis and present new data concerning the nature and transmission of the congenital form of the disease.

It has been known for almost half a century that toxoplasma is pathogenic. This was first demonstrated in mice by Nicolle and Manceaux,[1] and since 1909 the organism has been found in warm-blooded creatures on all continents except the Antarctic. In 1923 Jankû[2] gave the first description of human infection, in an eye from a hydrocephalic infant. Wolf, Cowen and Paige[3, 4] described congenital toxoplasmosis in newborn human infants and showed that the mother, although usually asymptomatic, contracts and transmits the infection. For serologic diagnosis, Sabin and Feldman[5] have established testing by complement fixation and by employing inhibition of methylene-blue staining of stock toxoplasma organisms by appropriate serums — this is commonly called the "dye test."

In 1940 Pinkerton and Weinman[6] first described a symptomatic case of toxoplasmosis in an adult — a twenty-two-year-old Peruvian who died of this infection and who also suffered from bartonellosis. Later, Pinkerton and Henderson[7] reported 2 cases in adults, in whom the disease resembled an acute rickettsial infection, with atypical pneumonia and hemorrhagic skin lesions. Guimaraes[8] and Sabin[9] presented 3 cases of acquired toxoplasmosis. Independently, they described acute meningoencephalitis, with and without localizing signs, associated with lymphadenopathy and splenomegaly. Two of the 3 patients died, and 1 recovered completely.

Syverton and Slavin[10] reported 2 cases in adults, in 1 of which the diagnosis was made by muscle biopsy, the chief manifestations being primarily in the skin and eyes. Callahan, Russell and Smith[11] described toxoplasma in a soldier who had encephalitis, an enlarged spleen and x-ray evidence of areas of bone destruction. Kass et al.[12] studied a sixty-year-old woman with meningoencephalomyelitis and polymyositis. The diagnosis was established by muscle biopsy, serologic tests, animal inoculation and autopsy. The symptoms and signs were so widespread that a preliminary diagnosis of diffuse collagen disease was made. Streptomycin, aureomycin, chloramphenicol, penicillin, ACTH, sulfadiazine and chloroquine were administered, without improvement.

A new form of toxoplasma infection, assumed to be acquired, was reported in 1951 from Copenhagen by Siim.[13] Patients with fever, generalized lymph-node enlargement and other clinical features of infectious mononucleosis were studied. Seven were found who had significant serum antibody titers by the complement-fixation and the Sabin–Feldman dye tests. Six patients were children, and 1 was an adult; 5 cases appeared in 2 small family outbreaks. All the patients experienced long convalescence and complete recovery. Jacobs,[14] while working with experimental toxoplasma infections in animals at the National Institutes of Health, contracted a febrile illness resembling infectious mononucleosis. During its course his serum antibody titers rose abruptly above old control levels.

Wilder[15] recently reported 53 cases of toxoplasmic chorioretinitis. She found the organisms in eyes removed surgically from patients whose ages ranged from thirteen to eighty-three years. Rodney and Mitchell[16] and Frenkel and Friedlander[17] recently compiled clinical and pathological data on congenital toxoplasmosis. Most of the cases in their series embodied the classic features of chorioretinitis, cerebral calcification, convulsions and hydrocephalus. Freeman and Pryor[18] observed such a case with long survival and mental retardation.

*Assistant attending pathologist, Hartford Hospital.
†Assistant attending pediatrician, Hartford Hospital.

Case Reports

Case 1. *Mother.* Mrs. P. F. (H. H. 668-062) was born and had lived in New Jersey. She had had a normal baby in 1948 and the subsequent pregnancy had been normal except for spotting during the 6th month. She and her husband were Rh negative.

Child. The patient was born by vaginal delivery in northern New Jersey in June, 1950. The birth weight was 2430 gm. At the time of discharge from the hospital the only finding was ptosis of the right eyelid.

During the 4th week of life the infant started to vomit. Her skin was pale, and she did not gain weight. During the 5th week there was weight loss and continued vomiting, the head enlarged, and the cry was high pitched. There was opisthotonos and she was unable to suck on a bottle.

Physical examination on admission to the Hartford Hospital on July 31, 1950, early in the 6th week, showed a dehydrated and sluggish infant, lying with back arched and head turned to the right. The right eye was closed, and the right side of the mouth drooped. The anterior fontanelle bulged, the head was enlarged, and there was palpable separation of the cranial-bone sutures. Deep tendon reflexes were hypoactive, and the sucking reflex was almost absent. The heart and lungs were normal; there was no enlargement of liver or spleen. There was a suggestion of nuchal rigidity.

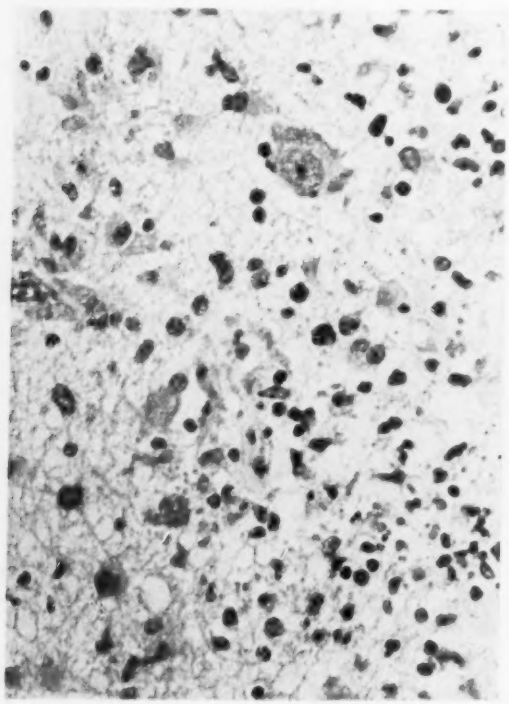


Figure 1. *Section of the Brain in Case 1 (Hematoxylin and Eosin Stain X250).*

The temperature at the time of admission was 99.6°F., and thereafter it fluctuated widely.

Urinalysis was negative. Examination of the blood revealed a hemoglobin of 9 gm. per 100 cc. with a hematocrit of 25 per cent, and a white-cell count of 7000, with an unremarkable smear and differential. The sedimentation rate (Westergren method) was 110 mm. per hour. The nonprotein nitrogen was normal. At spinal puncture the fluid was xanthochromic and under a pressure equivalent to 80 mm. of water. It contained 200 crenated red cells per cubic millimeter; the total protein concentration was 2900 mg. per 100 cc., and the specimen coagulated at room temperature. Fluid obtained at coronal suture taps was essentially the same. Cultures of these specimens were sterile. X-ray films of the skull showed increased intracranial pressure and fine, sparse intracranial calcification.

After 1 week of hydration and gavage feeding, the patient seemed to improve. On the 10th day, burr holes were made through the right parietal bone, and a thin, cystic cortex was uncovered. Beneath it the dilated occipital horn of the ventricular system was filled with pale-yellow, mucoid material. The patient died on the 15th hospital day.

At post-mortem examination* the body was well developed but poorly nourished and dehydrated. There were no anomalies. The thoracic and abdominal organs exhibited basal congestion of the lungs, blood-tinged mucus in the bronchial tree, and gastromalacia, with sloughing of the entire fundus. With the calvarium removed, the cerebrospinal fluid was seen to be hemorrhagic, turbid and full of fibrin particles.

Some of the cerebral gyri were enlarged, others were smaller than normal, beneath a thickened pia-arachnoid layer. There were patches of necrosis in the cerebral cortex 1 sq. cm. or less in area. At the parieto-occipital regions the pattern of gyrus and sulcus was destroyed, the brain surface presenting as a firm, gray membrane with only irregular flecks of cerebral tissue visible beneath the leptomeninges. On gross section there were many small gelatinous cysts in the white matter of both frontal lobes. The anterior horns of the ventricles were normal, but the occipital horns were enlarged to form porencephalic cysts up to 8 cm. in diameter. The overlying "cortex" was thin and friable; in many areas the cyst walls were formed by leptomeninges. Throughout the brain there were small areas of yellow-white, granular necrosis, which was especially prevalent near the ventricles.

Microscopical examination showed the brain lesions to be chronic and destructive inflammation. The larger necrotic areas were brain débris, nuclear fragments and calcium flecks of all sizes. Surrounding these was a reactive zone of glia, lymphocytes and lesser numbers of polymorphonuclear and eosinophilic leukocytes. Satellite nodules of glia and leukocytes near the larger necrotic areas contained small groups of toxoplasma organisms. Some of the groups of pseudocysts had ruptured (Fig. 1), and one could see small groups of 2 to 4 organisms lying free. Individual organisms could not be identified with certainty. The meninges near the involved parts of the brain contained cellular exudate of polymorphonuclear leukocytes, lymphocytes and eosinophils, in which a few toxoplasmas were seen. A few small meningeal vessels were thrombosed, but there was no evidence that this was caused directly by toxoplasma.

There was no microscopical evidence of visceral infection by toxoplasma. The eyes were not examined.

The final diagnoses were congenital toxoplasmosis, with chronic suppurative meningoencephalitis, porencephaly and hydrocephalus, dehydration and malnutrition, and microphthalmus, right (clinical).

The family had twin dachshunds as house pets. At about the time of conception of this infant, the male dog had "brain fever" followed by residual partial paralysis of a hind leg. The female dog remained healthy. Blood samples were taken from the patient's mother and from the dogs about four months after the delivery. The mother's serum showed a dye-test titer of 1:4096, and the affected male dog's serum a titer of 1:256, the healthy female dog's serum contained no antitoxoplasma-immune bodies.[19]

Case 2. *Mother.* Mrs. A. P., (H. H. 700-623), a 33-year-old woman, was born in Massachusetts. She had 2 normal children, and had not had miscarriages. Blood serologic findings were negative. When approximately 2½ months pregnant she contracted a febrile illness. There was continuous, generalized, headache for 2 days, and a dry cough that became more severe and more painful for 1 week, after which it gradually subsided. There was aching in the muscles and joints. These symptoms made her stay in bed. The posterior cervical lymph nodes became enlarged and tender, remaining palpable for about 3 months. She consulted a physician, who prescribed "grippe pills" and

*H.H. Autopsy 6680, performed by Dr. Carlos Vizcaino.

penicillin. He found that her left ear was draining. An otolaryngologist "removed some infected material" and gave local treatment. She improved, but was distinctly ill for about 10 days. During the remainder of the pregnancy she was pale, tired and haggard. She was often nauseated and lost her appetite. She stated that this fetus was less active than the 2 previous ones. She weighed 159 pounds at the 10th week of pregnancy and 153 pounds at the 30th week.

Child. On July 29, 1951, at the 33rd week of gestation, the mother went into spontaneous labor, and after 8 hours an easy breech extraction of a female infant weighing 1710 gm. was achieved. The infant had a loud cry and was well formed. The skin was jaundiced, parchment-like and dusky. There were countless macules and hemorrhagic spots over all parts of the body. There was fulness of the left side of the neck because of subcutaneous extravasation of blood. The spleen, liver and axillary lymph nodes were enlarged. The lungs were fairly well expanded, but breathing was labored, and the abdomen was distended.

The total nucleated cell count was 35,000 per cubic millimeter. A blood smear showed 2 per cent segmented and 15 per cent nonsegmented granulocytes, 15 per cent metamyelocytes, 8 per cent myelocytes, 8 per cent blast cells, 29 per cent small and 13 per cent large lymphocytes and 10 per cent eosinophils. Platelets were extremely rare, not more than 1 or 2 per 25 oil-immersion fields being seen. Nucleated erythrocytes were 131 per 100 white cells. Of these at least 50 per cent were at the basophilic, normoblastic stage or earlier. There was mild to moderate anisocytosis, poikilocytosis and basophilia, as well as large numbers of smudge and basket cells. The smear so resembled those of infants with severe erythroblastosis due to blood-group isosensitization that a direct Coombs test was performed on the infant's blood. This test was negative. Both mother and infant were Group A, Rh positive. The infant was critically ill from the outset, and died 13 hours after delivery.

At post-mortem examination* the scleras were yellow and jaundice and cutaneous hemorrhages were noted. Bloody foam was found in the nose and mouth. The abdomen was swollen, and the fontanelles bulged. There were no deformities. There were 5 cc. of clear fluid in the pericardium, 30 cc. of bloody fluid in each pleural cavity and 50 cc. of similar fluid in the peritoneal cavity. Hyperemia and petechiae were observed in the mucosas of the respiratory, gastrointestinal and urinary tracts, as well as small hemorrhages in the lungs. The liver weighed 100 gm. (normal, 66 gm.), and the spleen 42 gm. (normal, 4 gm.). The linings of the blood vessels were jaundiced. The viscera were otherwise normal, and the eyes were grossly normal.

The brain was swollen, compressed and yellow. There were small hemorrhages and petechiae in the meninges and on the surfaces of the hemispheres. There were areas of necrosis, some of them caseous in appearance, up to 1 cm. throughout the brain. The ventricles were dilated and contained a little fresh, clotted blood. An x-ray film of the removed brain showed diffuse, fine calcification. Cultures of heart's blood and spleen were sterile.

Microscopical examination of sections of the brain showed chronic destructive inflammation. The normal structures were largely replaced by areas of necrosis in which polymorphonuclear leukocytes, lymphocytes, eosinophils and flecks of calcium were present. Many typical pseudocysts of toxoplasma were found at the margins of the necrotic areas and in comparatively uninvolved regions. There were patchy areas of inflammation in the meninges. In the eyes, there was diffuse inflammation and calcification in the retina and the inner layers of the choroid. The cellular and fiber layers of the retina were completely obliterated.

In the myocardium there were foci of chronic inflammation, in which a single pseudocyst of toxoplasma was found. Tiny zones of inflammation were seen in the liver, pancreas, spleen, skin and skeletal muscle, without toxoplasma.

The final diagnoses were congenital toxoplasmosis, with chronic meningoencephalitis and myocarditis, chorioretinitis, myositis and dermatitis (toxoplasma not demonstrated), causing erythroblastosis fetalis, with hepatomegaly, splenomegaly, jaundice and widespread petechial hemorrhages.

Serologic Data

On December 12, 1952, Mrs. A. P. was delivered of a healthy, full-term female infant. Serial specimens of blood and a single specimen of spinal fluid were taken from members of the family. The dye-test titers, all performed at the same laboratory,[20] were as shown in Table 1.

The mother's serum continues to exhibit a high antibody titer. Her antibody does not appear in her spinal fluid in significant quantity, but it does pass through the intact placenta, and at the time of delivery was found at the same dilution in the second infant's serum. The fall in healthy infants' serum titer to 1:256 supports the contention that it is unaffected and has only passive transfer antibodies, although it is disappearing less rapidly than expected.[20]

TABLE 1. *Dye-Test Titers on Members of Family.*

DATE	FATHER'S BLOOD	MOTHER'S BLOOD	MOTHER'S SPINAL FLUID	AFFECTED CHILD'S BLOOD	HEALTHY CHILD'S BLOOD
	titer	*titer*	*titer*	*titer*	*titer*
Sept., 1951	1:32	1:16384	—	1:4096	—
Dec., 1952	—	1:4096	1:4	—	1:4096
May, 1953	—	1:4096	—	—	1:256

FIGURE 2. *Toxoplasma — Infected Placenta from Case 2, with Two Normal Placentas for Comparison.*

Animal Inoculation

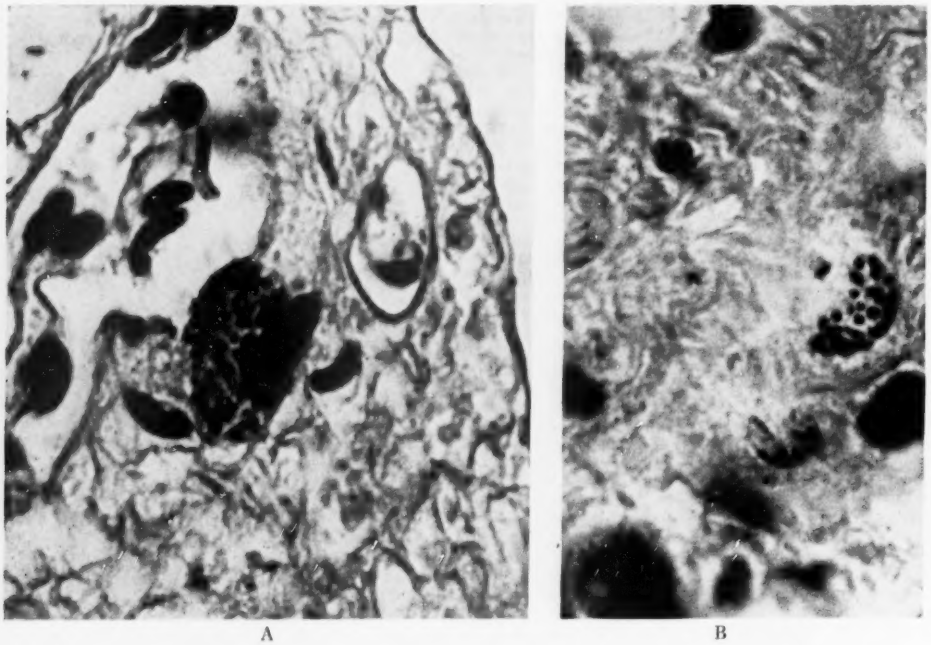
A specimen of blood from the affected infant was inoculated into immature white mice and carried for three blind passages. Ascites did not develop, and toxoplasma could not be found. Pigeons, squirrels and rats lived around the family's home. Mouse passage and histologic examination of tissues from a large Norway rat trapped on the premises were negative for toxoplasma.

Placenta

We received the placenta of the affected pregnancy (H. H. Surgical 128003). It was saved be-

*H.H. Autopsy 7151, performed by Dr. Alexsandra Vitolins.

cause it seemed pale and friable (Fig. 2). It weighed 380 gm. after fixation and removal of several blocks for section. The umbilical cord was discolored (yellow-green), and the entire specimen had a slightly foul odor. The fetal surface was not remarkable, but on the maternal side the tissues were soft, stringy, friable and granular. The cotyledons were not distinct, and instead of being circumscribed they were shaggy and irregular. On section, the chorionic villi were large and often stained weakly. Their stroma was loose and edematous; the Langhans cells were intact, and the syncytial cells were gathered into multinucleated knots on the surfaces of the villi. The fetal vessels contained nucleated erythrocytes, but there was no erythropoiesis in the villi.



A B

FIGURE 3. *Pseudocysts of Placenta in Case 2 (Hematoxylin and Eosin Stain X1200).*
A delicate capsule is visible about the oval cluster of organisms (A), *which are uniform and show a few perinuclear halos. A crescentic pseudocyst of toxoplasma is observed* (B). *Individual organisms are more varied in size and shape than those in* A.

Two typical pseudocysts of toxoplasma were found in the placenta (Fig. 3). They were within villi and were not accompanied by active inflammation. Small calcifications were found in many areas. It is not clear whether calcification is of significance in association with toxoplasmosis, since it is often seen in human placentas. It appeared in x-ray films of this placenta as fine granular and "soft" opacities. This finding was compared with calcifications appearing in films of placentas taken at delivery of normal infants. It is the opinion of several experienced radiologists that the pattern of calcification seen in the films of the toxoplasmic placenta was not characteristic.

This is the third recorded demonstration of toxoplasma in the human placenta. Neghme et al.,[21, 22] of Santiago, Chile, found toxoplasma in 2 of a group of 85 placentas examined because of abortion or stillbirth. The 2 significant placentas were obtained about thirty weeks after stillbirths, 1 fetus being macerated and the other exhibiting multiple congenital anomalies. There was no description of the fetal tissues. A dye test on the serum of one of the women gave a titer of 1:400; from the other the titer was 1:1024. Together, these 3 cases verify the assumption, made from clinical data and experimental infections in animals[23] that transmission of toxoplasmosis from human mother to human fetus is by the placenta rather than by fetal membranes or amniotic fluid.

While studying our 2 cases of the disease we inquired about cases of toxoplasmosis at several nearby hospitals. From Norwalk, Connecticut, Barnett[24] recently reported a case of congenital toxoplasmosis. Vaughan[25] mentions a case resembling erythroblastosis fetalis in New Haven, with survival. Netsky[26] described 2 cases of fatal congenital toxoplasmosis at the Montefiore Hospital

in New York City. The Children's Medical Center[27] has had 7 cases during the last decade that are considered to be toxoplasmosis. Kass et al.[12] reported a case of adult toxoplasmosis from the Boston City Hospital. This effortless unveiling of 12 cases of the disease persuades us that many more exist.

Discussion

Examination of personal and published cases has suggested to us the following classification of toxoplasmosis: Type 1, asymptomatic infection; Type 2, mild grippe-like infection (chiefly serologic evidence); Type 3, infection simulating infectious mononucleosis (chiefly serologic evidence); Type 4, toxoplasmic chorioretinitis; Type 5, adult symptomatic infection resembling typhus fever, meningoencephalitis or diffuse collagen disease; and Type 6, congenital infection, with signs of either erythroblastosis or central-nervous-system damage predominating. Congenital toxoplasmosis, transferred from mother to fetus during pregnancy, is usually a distinctive entity with ocular and central-nervous-system involvement. In a few cases, such as our Case 2, there is evidence of wider systemic involvement. Acquired toxoplasmosis is much more versatile. Types 1, 2 and 3 are acute and apparently self-limited forms of the disease. In Types 4 and 5 there may be infection of a specific organ or wide systemic involvement, but in either event permanent damage occurs. These cases represent acute and chronic acquired toxoplasmosis. The complex and unsettled questions concerning sources, routes of entry and pathogenesis of acquired human infections are not discussed here.

Type 1 (Asymptomatic Infection)

This type is represented by a group of people with positive skin and serologic tests. Some are the mothers of infected infants, and others are discovered in surveys. Sabin and Feldman[20, 28] and Jacobs[14] found in population surveys that the percentage of persons with positive skin and serologic tests increased with age.

Type 2 (Mild Grippe-Like Infection)

This group includes the nonspecific clinical states that are related to toxoplasmosis by circumstance and by serologic evidence. The literature contains several accounts of so-called grippe during significant pregnancies. The experience of Mrs. A. P. (Case 2) is typical of this sort of event. We suspect that some of these minor illnesses assume the same relation to florid toxoplasmosis that nonparalytic poliomyelitis and primary tuberculosis bear to their advanced counterparts.

Type 3 (Infections Simulating Infectious Mononucleosis)

Serologic evidence that toxoplasmosis may mimic infectious mononucleosis has been collected by Siim[13] and Jacobs.[14] This form has been observed in families and in persons working with toxoplasma in the laboratory. It is a mild disease, with slow convalescence and complete recovery. Toxoplasmas are not demonstrated, but the Paul–Bunnell tests are negative.

Type 4 (Chorioretinitis)

Toxoplasmic chorioretinitis, except in newborn infants, first appears as a chronic, smoldering infection.[29, 30] The destructive lesions result from rupture of the pseudocysts and probably from a local sensitivity reaction to liberated antigen, although involvement of other parts of the body is usually not demonstrable. The younger the patient, the more likely the occurrence of central-nervous-system involvement. We suspect that in adult chorioretinitis, as described by Wilder,[15] the eye is the only significant localizing site of an otherwise mild and self-limited infection.

Type 5 (Acquired Systemic Infection)

This category includes adults and children with signs and symptoms of widespread disease. We divide them into three groups. The first resembles an acute rickettsial infection, with hemorrhagic skin rash and pneumonitis; the infection is severe, does not respond to treatment and is usually fatal. The second type is present clinically as encephalitis without visceral involvement or chorioretinitis; this form is rare. In the third variety a febrile course with symptoms of involvement of multiple organ systems simulates widespread collagen disease, as illustrated by the patient of Kass et al.[12]

Type 6 (Congenital Infection)

There are two forms of congenital toxoplasmosis. In the first, and more common, there is fever, vomiting, convulsions, progressive hydrocephalus, chorioretinitis and cerebral calcification. Some of these infants die promptly, and others live for months or years with permanent cerebral and ocular defect. Studies by McKhann[31] indicate that a number of children with mental retardation and convulsions have significantly high antibody titers.

The second and rarer form of congenital toxoplasmosis can be confused with erythroblastosis due to blood-group isosensitization. This is not surprising if one remembers that congenital infections, including congenital syphilis, were known to be a cause of erythroblastosis fetalis long before the role of the blood-group factors was discovered. The blood smear and clinical course are identical with that seen in other forms of erythroblastosis. This form of congenital toxoplasmosis is exemplified by Vaughan's[25] case, our own Case 2, and a case reported by Callahan et al.[11] We suggest that the Coombs test be used in distinguishing erythroblastosis caused by congenital infections from that caused by blood-group-factor sensitization.

Summary and Conclusions

Toxoplasma has been recognized for about fifty years, and knowledge of its ability to cause human disease is increasing. Serologic tests are now available for increasing and improving the diagnosis of toxoplasmosis. The Sabin-Feldman dye test is indicated in the following circumstances: encephalitis of unknown cause; "infectious mononucleosis" with negative Paul–Bunnell test; erythroblastosis fetalis with negative direct Coombs test and Landsteiner blood group incompatibility ruled out; infections of unknown cause during pregnancy; and chorioretinitis.

A casual survey among eastern hospitals has revealed 10 unreported cases of toxoplasmosis.

Two cases of congenital toxoplasmosis are described. One of them closely resembled erythroblastosis fetalis. A study of home contacts in the first case suggested transfer of the infections from dog to human being. Involvement of the placenta by toxoplasma was demonstrated in the second case.

Effective treatment of toxoplasma infections is needed.

We are indebted to Mr. Peter DeParolis and Mr. Antol Herskovitz for the photographs.

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PSYCHIATRIC RESEARCH IN A GENERAL HOSPITAL*

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THE Psychiatric Unit attached to the Medical Service has been in operation at the Peter Bent Brigham Hospital for seven years.‡ During the first five years, experimentation with the teaching of so-called "integrated" medical practice led to certain conclusions concerning what should be taught and how best to teach it.[1] Integrated medicine attempts to balance specialization by reviving the attitude of the family physician. Interest is focused on the patient afflicted with disease rather than on a disease illustrated by a patient.

The members of the Psychiatric Unit serve as consultants on the medical and surgical wards. They also help to supervise medical students and house officers in the general medical outpatient department, where it has been found that even though their presenting complaints are usually physical symptoms, about 70 per cent of the patients require psychologic understanding more than any other treatment. The young physician is given assistance in shaping his treatment program in such a way that certain limited goals can be achieved within the available time, which usually consists of not more than half a dozen visits.

A good psychiatrist, like any other good doctor, relies to quite an extent on the art of treatment. The practice of this art can be encouraged and developed, although there is, of course, a considerable difference in the temperamental capacity of individual physicians. In recent years a fund of well established knowledge has accumulated concerning normal emotional development from infancy to maturity. It has been found possible to make a considerable amount of this information available to nonpsychiatrists, many of whom seem able to use it effectively.

First-year medical students are now given lectures on normal emotional development. From time to time lectures are given to the house staff on topics such as the hysterical character as it is encountered on a general medical service, with particular stress on the patient's utilization of hospital procedures and contacts with doctors to reinforce magical fantasies or nightmarish fears. The use of compliance and "correct behavior" as ways in which a patient with an obsessive character structure deals with hostile impulses is shown to affect his capacity for carrying out any regimen prescribed by the doctor, usually resulting in literal obedience with an undercurrent of destructive rebellion. The influence of pathologic guilt feelings on health and the dangerous effects of hostile impulses turned against the self are illustrated by bereavement, depression and suicide. The psychologic background for the pathologic use of food, drink and drugs is explained in terms of what may often constitute a malignant regression to infantile dependent and destructive urges as seen in some forms of alcoholism, in addiction to narcotics, and in some of the obesity problems.

Physicians have always been aware of the possibilities for helping their patients through the special qualities of the personal relation between the patient and the physician. A knowledge of the patient's biography often provides an understanding of the personal significance of the physician as a substitute parent or sibling and an awareness of what this means to the patient often makes it possible for the physician to be more helpful. It may also explain certain difficulties encountered in obtaining the patient's logical co-operation.

Quite a number of the young physicians have called attention to illogical feelings of their own about their patients that sometimes result in a certain uneasiness. By and large, these difficulties are not greatly different from those of any other professional person who has to deal in an intimate way with another human being.

One house officer, for instance, explained that it was not easy for him to talk to a patient older than himself. He was uncomfortably conscious of his youthful appearance and reported that 1 patient in 5 commented on his being too young to be a doctor. Another house officer stated that when a patient demanded specific examinations or tests he himself became anxious, and he also became overly disturbed if anyone complained that he had not received adequate treatment; as soon as the patient showed some therapeutic response the house officer felt more secure and was able to deal with the patient more comfortably.

During a teaching session one house officer seemed to have great difficulty in describing an older woman. He suddenly burst out with the statement that he found himself immediately hostile to dominating, aggressive women like this patient. During further discussion he explained that he felt especially sympathetic to the underdog, and liked to work with patients who had difficulties similar to his own. Although this led to his trying to make as sure as possible that he gave his patients their money's worth, he tended to devalue his own capacity to be of help. His overidentification proved to be

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disadvantageous on one occasion, when he was unable to prescribe a necessary diet, explaining, "I would not be able to put myself on one." A very conscientious house officer, on the other hand, was worried about asking patients any personal questions and seemed to think that this was much too aggressive. He later confessed that his own policy was to tell a person as little as he could about himself, believing that then no one would be in a position to make use of any information to hurt him.

When a young physician has the opportunity actually to experience and to become more fully aware of the way in which his own feelings enter into the treatment situation, he is considered to have made an important advance in his personal and professional development. If he can also gain an increased appreciation of the personal meaning of physical symptoms that may or may not have resulted from structural organic changes, he will be in a much better position to treat the majority of patients who consult an internist in practice.

Typical patients seen on any day in the medical outpatient department included a thirty-eight-year-old cab driver who had been vomiting for four days. His wife was seven years his senior. He was deferred from Army service because of "emotional instability." He was quite anxious and had a head tic. He reported that he quarreled and argued with his wife, but was evidently quite dependent on her. His symptoms apparently developed in the setting of a recent discussion with her. The gastrointestinal series was negative. He rapidly established a confiding relation to the fourth-year student, and his symptoms disappeared.

On the same day a sixty-four-year-old widow came in complaining of palpitations of the heart and "weak feelings" for the past eighteen months. Her symptoms appeared after breakfast and occasionally after lunch. A subtotal gastrectomy had been carried out two years previously for ulcer, and her symptoms were apparently related to the dumping syndrome. She explained that she had felt "extremely nervous" since divorce from her second husband a few years before the interview, and she believed that the ulcer had developed in that setting. She lived alone with her single sister, about whom she "worried." She responded well to frequent small meals with high-protein content and expressed friendly feelings toward the student, preferring to take a diet he would prescribe rather than to accept referral to a female dietitian.

Discussion of the symptomatic improvement in these cases gave the student an opportunity to appreciate the therapeutic effect of his personal understanding of the situation. This promoted a healthy growth of his professional self-confidence, and he could see that diets and medicines can be much more effective when the patient is confident that the doctor really knows him as a person.

During the past two years integrated medical practice has been supplemented by integrated medical research. Collaboration of psychiatrists trained in psychoanalysis with surgeons and internists with a background in the basic medical sciences has required a mutual understanding of working methods. Psychiatrists are familiar with methods that elucidate the reaction to present stimuli in terms of what these stimuli mean to the patient because of his past experience. Those trained in the basic medical sciences rely chiefly on measurement rather than on symbolism and meaning. Psychiatrists are accustomed to the study of multivariables and have been trained not to interfere with the flow of the patient's thoughts and feelings, whereas the basic scientists rely to a large extent on planned interference modeled on the laboratory experiment, which attempts to eliminate or "control" all the variables except the one being studied.[2] These contrasts in emphasis concern the nature of the phenomena being studied rather than any basic difference in scientific attitude. All scientists are searching for what has been described as "relevant truth" by the method of objective observation. Setting up a crucial experiment requires imagination and the intuitive selection of focus. Although neither intuition nor imagination is unscientific, all scientists know that they must be constantly self-critical to distinguish private fantasy from objective fact. The psychologic worker is particularly aware of this, sees the contrast in his daily therapeutic work with patients and has been trained to a special degree of alertness to the effect of his own emotional preoccupations on what he is trying to observe.

The principles of prediction and statistical measurement are applicable to all scientific research.[3] It is evident, however, that an increase in the number of variables requires much greater modesty about what can be predicted. Measurements that can be carried out are always welcome, but statistical results can be confusing rather than helpful unless it is possible to establish a clear definition of the units being counted.

Some of these problems are illustrated by the observations made on a thirty-two-year-old bulldozer operator who was admitted to the hospital because of hypertension and congestive heart failure. In recent years he had lived with a sixty-two-year-old half-sister, to whom he had transferred his feelings of dependence on his mother, accompanied by a good deal of resentment at being so much tied to her apron strings. The social worker corresponded with this half-sister to learn more about the family background.

After a study of the patient's cardiovascular and renal function, it became evident to the physicians in the metabolic group that he could not be expected to live for more than a few months. He had been rejected at another hospital as too poor a risk for sympathectomy. Bilateral total adrenalectomy was

now proposed in the hope that removal of the adrenal influence on blood pressure and substitution of the artificially synthesized cortical substances (desoxycorticosterone acetate and cortisone) in dosages that could be varied according to his physiologic needs might offer a chance of prolonging his life.

The cardiovascular studies involved a wide variety of measurements, including "basal" blood-pressure determinations. His blood pressure was taken under sedatives to determine the degree to which it varied when psychologic tensions were minimized. The psychiatrist saw this patient daily during the period that all these tests were being carried out. During these interviews the patient had an opportunity to express his feelings about his illness, his hospitalization and the tests to which he was being subjected. His version of the "basal" blood-pressure determinations was tape-recorded as follows:

> Then one night they told me they were going to put me in the sack and tie me in. They didn't tell me they were going to tie me in, but they brought in the sides to the bed, and, of course, I'm looking at them things. Then I was in a single room with another guy; that was before I was moved out into the ward. Of course, I'm looking at those things and saying, "Jesus, I wonder what the hell's the matter with me now that they have to tie me in" — you know, put the bars up. I thought it was some kind of a test where they keep you asleep and try to keep you in a relaxed position and take your pressure all night long. I didn't know. I thought maybe I was getting worse or something and that they really were going to try something out to see if they could bring me out of it. I didn't know it was a test at the time. Of course, the girl when she came in, she said, "Now don't worry about these things," she says, "This is nothing." That don't mean nothing to me. When I see bars going up around the bed I still figure it's something.

This patient repeatedly expressed himself as "holding it in," which referred not only to his feelings of anger but also to a primitive conception of his body as a highly vulnerable barrier between himself and the outside world. Further associations in later interviews abundantly confirmed this, and it became evident that hypodermics that penetrated the skin, medication entering his mouth, enema tubes penetrating his rectum and the introduction of a catheter into his urethra were all experienced as dangerous assaults with the implication that he himself was passively helpless. On several occasions, furthermore, he actually developed pulmonary edema requiring emergency treatment at times when he was frightened by the anticipation of certain test procedures. His reaction in this regard was particularly significant in view of the fact that some of the tests to which he reacted so strongly were what turned out to be unsuccessful attempts to determine his basal or resting status. He was able to express these fears of which he felt ashamed to the psychiatrist during subsequent interviews because of the relation that had been established.

This patient, whose kidneys had been badly damaged by the progress of his disease, did not do well postoperatively, and this was reflected in the various tests of renal and cardiovascular function, which did not show the hoped-for improvement in comparison to the preoperative situation. During his later interviews he was drowsy and several times actually fell asleep. The rise in his nonprotein nitrogen indicated that physiologically he was approaching uremic coma. Since it was known from his preoperative interviews, however, that "playing possum" was one of his usual ways of dealing with certain unpleasant situations, the question came up whether his falling asleep might to some extent represent a postoperative change in his psychologic attitude toward the interviewer, to whom he had previously talked fully and confidingly. This was one of the many situations in which it was helpful to call on the psychologist, who had been added to the research team. He found postoperatively that there was indeed a significant change in the patient's attitude as revealed by the Rorschach and other psychologic projections tests.[4] His former interest in the future had disappeared, and there was a definite increase in distrust and suspicion of the doctors that may have arisen from his unspoken awareness of the fact that he was actually dying.

This patient was one of a number on whom bilateral total adrenalectomy was carried out. It soon became evident that he, like many of the other candidates for this operation, was intensely responsive to the vicissitudes encountered by those who had already been through it. The patients spontaneously formed what they called the "Adrenalectomy Club," and any serious mishap to one of the members was sensitively reflected in the psychologic attitudes of the others.

The sociologist who studied the ward as a social system was much interested in the meaning of the club to the individual members. She made her observations by spending all day and much of the evening on one of the wards of the hospital over a period of several months. The patients knew that she had no therapeutic relation to them, and this made it possible for them to talk with unusual freedom about their feelings concerning the doctors, the nurses, the hospital and the research program.

Integrated medical research refers not only to the fact that surgeons, internists, psychiatrists, psychologists, sociologists and social workers make observations having to do with the same patient. In fact, these observations would not only disturb the patient but also confuse the results unless it were possible to establish an effective integration of quantitative and interpretive methods. In recent years the concept of stress has been useful as a way of referring to the psychologic as well as the biologic responses of the total organism. Integrated research requires a critical appreciation of the degree to which biochemical and other physiologic determinations must be evaluated in the light of the psychologic setting in which these measurements are made.

Bilateral total adrenalectomy is, of course, a serious operation, and postoperatively the patient

becomes totally dependent on artificially synthesized substances that replace the activity of the adrenal glands. Comparative studies have been carried out on patients subjected to a different and equally serious operation that does not require substitution therapy. Patients undergoing mitral-valve surgery have provided an unusual opportunity for the study of acute and chronic stress.[5] It became evident that an understanding of the long-term adaptation to progressive limitation of activities provided the necessary background for the recognition of emergency defenses as they developed in the hospital situation both before and after operation. Integrated research at this hospital has also included the study of the psychologic responses to cortisone and ACTH in a large variety of cases.[6] It has been found that investigation of the clinical effects of these substances makes it possible to explore the biochemical sources of instinctual tension and thus provides a new and promising approach to an understanding of personality structure.

The present-day interest of surgeons in the physiologic processes of homeostasis and the medical advances in the understanding of the dynamic biochemical balances concerned with immunity and growth have made it increasingly necessary to develop technics for investigating the behavior of the total organism rather than of an isolated part. Integrated research, including observation of psychologically meaningful activity, has opened new vistas for medical and surgical progress.

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THE THEORY AND PRACTICE OF PUBLIC HEALTH

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RAPID developments in the theory and practice of public health in the past decade have been brought about by the discoveries in the medical sciences, by the changing pattern of community organization and finally by the relatively decreased importance of infectious diseases as compared with chronic illness. In 1948 the American Board of Preventive Medicine was incorporated, thereby giving public health an equal status with others specialties of medicine. The public, as well as the medical profession, has become more conscious of public-health programs. The health education programs of the medical societies, health departments, insurance companies and the public press have impressed upon people the desirability of maintaining good health.[1] The stimulus of the passage of the Social Security Act, making federal grants-in-aid available to states and localities, has played a large part in the extension of public-health programs.[2] The purpose of this presentation is to analyze factually the progress in public health that has been made in the last decade.

Health Expenditures

National

The average annual expenditure for civilian health and medical services for the past twenty years amounted to approximately 4.3 per cent of the country's net product. By 1951 this totaled $13,600,000,000, or $89 per capita. Direct payments by the consumer amounted to 65.5 per cent, governmental expenditures to 19.6 per cent, and hospital construction to approximately 6.8 per cent, and the remainder was derived from philanthropy and industry.[3]

Only one penny out of each budget dollar of the federal Government was spent for civilian health activities during the fiscal year 1952-53, and most of this was allocated for medical and hospital services for veterans. Only a relatively small portion of the total governmental expenditures are utilized for public-health purposes; the Department of Health, Education and Welfare (formerly the Federal Security Agency) receives 21.6 per cent of federal expenditures for health for the operation of all its programs (Table 1), including the Public Health Service hospitals and health activities, as well as the Children's Bureau, Vocational Rehabilitation and so forth. Although governmental expenditures for all types of health services have increased rapidly in the last decade, much of this increase has been consumed by rises in costs due to the devaluation of the dollar and a simultaneous increase in the size of the population. It is thus estimated that during the period 1942-1950 there has been an adjusted increase of governmental services of 57 per cent in hospital services but only 29 per cent in health activities.

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State

For the fiscal year 1949 the states and territories spent $962,186,000 for health activities, but only 17.5 per cent of this was expended by health departments; 27.7 per cent was expended by special boards or commissions (usually for mental patients), 20 per cent by departments of welfare, and 10.1 per cent by departments of education, the remainder being spent by departments of Agriculture, Labor,

TABLE 1. *Obligations by Federal Agencies for Health Activities, Fiscal Year, 1950.**

AGENCY	AMOUNT	PERCENTAGE BY AGENCY
	$	
Veterans Administration	812,434,000	52.9
Department of Defense	331,005,000	21.6
Federal Security Agency	330,924,000	21.6
Department of Agriculture	18,525,000	1.2
Department of the Interior	16,967,000	1.1
Atomic Energy Commission	15,770,000	1.0
All other	9,104,000	0.6
Total	1,534,729,000	

*Based on the report of the President's Commission on the Health Needs of the Nation.

Boards of Control, independent state hospitals, state universities and other agencies of state government. This expenditure represented an outlay of $6.36 per person.

The per capita expenditures by states varied from a high of $13.57 in Washington to a low of $3.25 in Tennessee. In Massachusetts the figure was $7.99. The annual expenditures of state health departments increased from nearly $48,000,000 in 1940 to over $168,000,000 in 1950 — a rise of 251 per cent. After allowances are made for higher prices and wages, the actual total increase is only 76 per cent. During this period the expenditure for health-department purposes in Massachusetts rose from $3,793,000 in 1940 to $6,484,000 in 1950 (this includes the state health department's five institutions), an increase of 71 per cent. However, after allowance is made for higher prices and wages the total annual expenditure actually decreased 15 per cent. Only one state — namely, Delaware — had a worse record than Massachusetts in the change between the 1940 and 1950 annual health-department expenditure. In Delaware there was a reduction of 28 per cent.

Simultaneously, in Massachusetts the ratio of funds derived from federal sources rose approximately 7 per cent whereas for the country as a whole federal funds decreased by approximately 6 per cent. These data — the fall in the total expenditures of 15 per cent by the health department and the relative rise of 7 per cent in federal funds — indicate that the state legislature has not appropriated increased funds for health-department purposes that were generally made throughout the country. Although Massachusetts has prided itself for having the first state health department in the country from the point of view of its origin in 1869, from a financial point of view in the change between 1940 and 1950 it is next to the lowest in improving its services to the public.

Thus, it may be assumed that increases in services rendered by the Massachusetts Department of Public Health resulted from improvements of internal administration and improvements in economy rather than higher expenditures.

INFECTIOUS DISEASES

During the past decade the morbidity and mortality of the major communicable diseases has decreased (Table 2). Smallpox, for example, has not occurred in Massachusetts since 1933, and there have been no deaths from smallpox since 1927.

TABLE 2. *Comparison of Mortality Rates for Some Communicable Diseases in Massachusetts and the United States, 1901–1950.**

DISEASE	MORTALITY RATE, 1901–1905		MORTALITY RATE, 1916–1920		MORTALITY RATE, 1931–1935		MORTALITY RATE, 1946–1950	
	U. S. *per 100,000*	MASS. *per 100,000*	U. S. *per 100,000*	MASS. *per 100,000*	U. S. *per 100,000*	MASS. *per 100,000*	U. S. *per 100,000*	MASS. *per 100,000*
Diphtheria	29.4	29.2	15.0	17.1	3.9	1.8	0.5	0.6
Measles	8.8	7.5	9.8	9.6	3.1	3.1	0.5	0.3
Scarlet fever	11.2	10.0	3.6	3.5	2.1	2.3	0.4	0.03
Whooping cough	10.0	9.6	11.1	15.0	4.3	2.2	0.9	0.3
Smallpox	2.6	2.9	0.4	0.07	†	—	†	—
Typhoid	24.9	17.8	11.3	3.7	3.6	0.5	0.1	0.04
Tuberculosis (all forms)	158.7‡	219.7	135.8	137.3	60.4	51.9	28.9	29.2

*Based on *Vital Statistics of the United States.*

†Less than one tenth of 1 per 100,000 population.

‡Only pulmonary tuberculosis.

Typhoid fever and diphtheria are now so rare that medical schools have difficulty in finding sufficient teaching material. With the advent of the sulfonamide drugs and the antibiotics there are no longer complications caused by scarlet fever and other streptococcal infections. Such diseases as measles and infectious hepatitis, however, have continued to be as prevalent as in the past and may be expected to become apparently more common as reporting improves under the stimulus of the availability of gamma globulin for prevention or modification.

Infantile paralysis has apparently increased owing in part to better diagnosis and in part to better reporting. The ratio of nonparalytic to paralytic cases has continued to climb so that in many

states the number of nonparalytic now exceeds that of the paralytic cases.[4] The development of gamma globulin for the prevention or modification of poliomyelitis poses additional problems of distribution because of the limited amount available and the temporary passive immunity.[5]

Reports of health departments indicate that a higher ratio of the population is now protected by immunization. The development and free distribution of triple antigen against whooping cough, tetanus and diphtheria has been in part responsible for bringing more children into the offices of private practitioners for immunization. Massachusetts is one of the three states that offers biologic products for free distribution (Table 3). Similarly, Massachusetts was the first state to begin the production of blood fractions (1948) and has thus been able to set up a stockpile.

TABLE 3. *History of Distribution of Biologic Products in Massachusetts.*

PRODUCT	YEAR PRODUCTION STARTED
Diphtheria antitoxin	1895
Schick-testing outfits	1915
Tuberculin	1930
Diphtheria toxoid (fluid)	1932
Pertussis vaccine	1949
Tetanus toxoid	1949
Purified diphtheria toxoid	1949
Diphtheria and tetanus toxoids and pertussis vaccine ("triple vaccine"), aluminum phosphate precipitated	1949
Diphtheria and tetanus toxoids, aluminum phosphate precipitated	1949
Tetanus antitoxin	1950

During the past fifty years there has been a striking decline in the mortality from tuberculosis. The mortality rate of 194 per 100,000 population in 1900 was reduced by more than half in the first quarter of the century, by another 50 per cent in the next seventeen years and, finally, by 50 per cent in the last nine years. In other words the 1951 rate of 20.1 per 100,000 population was approximately one tenth of the rate prevailing at the turn of the century. Of greater significance is the fact that the most rapid decline in mortality has been within the last seven or eight years.[6]

The availability throughout the United States of more adequate sanatorium care, improved thoracic surgery and more recently streptomycin, dihydrostreptomycin, isonicotinic acid hydrazid and other drugs has been responsible for this improvement. In some states, such as Massachusetts, with an adequate number of available beds, waiting lists at the sanatoriums were due primarily to the shortage of nurses, which led to a closing down of whole wards or wings. Mass chest x-ray programs have resulted in early case finding and earlier hospitalization. Tuberculosis has shifted from a disease of major importance in young people to one of major importance in older men. It has dropped from the second leading cause of death in the United States in 1900 to eighth in 1950.[7]

Although mortality from tuberculosis has decreased in a remarkable fashion, morbidity decline has been less striking (Table 4). In fact, during World War II an actual rise in the number of new cases reported was noticed, but after a peak had been reached in 1948, the number of new cases reported began to decline again. The number of new cases reported in 1951, however, was still somewhat higher than that reported in 1940. Prevalence during the last decade appears to have remained high, probably because of two factors: more extensive case finding, leading to a higher percentage of known cases; and improved therapy, resulting in a longer life for patients with tuberculosis.[8]

TABLE 4. *Tuberculosis Morbidity and Mortality, United States and Massachusetts, 1941–1951.**

YEAR	UNITED STATES			MASSACHUSETTS		
	NEW CASES REPORTED	CASE RATE *per 100,000*	DEATH RATE *per 100,000*	NEW CASES REPORTED	CASE RATE *per 100,000*	DEATH RATE *per 100,000*
1941	105,714	79.5	44.4	3,282	75.2	37.4
1942	117,221	89.6	43.7	3,274	75.6	37.3
1943	118,042	88.0	41.9	2,960	68.2	41.6
1944	124,789	94.2	40.8	2,874	66.4	38.9
1945	117,400	88.2	40.1	2,839	62.9	36.3
1946	118,014	83.7	36.4	3,037	66.7	36.7
1947	133,837	93.0	33.2	2,795	61.3	34.5
1948	145,131	98.3	29.8	2,886	61.0	29.4
1949	131,973	88.7	26.1	2,589	55.6	24.1
1950	121,228	79.9	22.2	2,492	53.4	21.5
1951	118,438	76.4	20.1	2,293	48.4	18.7

*Data from the National Tuberculosis Association for the United States and the Secretary of the Commonwealth for Massachusetts.

Venereal diseases, which during every war increase in prevalence, have continued to decline rapidly since the advent of the sulfonamides and, more recently, the antibiotics. This lowered incidence has brought about a sizable reduction in the federal grant-in-aid program for venereal diseases to states. Since the beginning of federal grants-in-aid for venereal-disease control in 1938, when nearly $2,500,000 was appropriated, the amounts allocated to the states rapidly increased until a peak of over $16,500,000 was reached in 1947. Since that time, however, the appropriations have decreased so rapidly that less than one tenth of the peak amount has been recommended for the 1953-1954 budget.

The treatment of venereal diseases is now usually ambulatory, and many patients are treated by private practitioners rather than in public clinics. Because of the decreased duration, lower cost and more efficient services, patients obtain treatment from private practitioners, who at times are reluctant to report cases. Therefore, the reporting in most states is less complete than in the past, except in states where special efforts have been made to improve systems of case finding and reporting.[9]

Although malaria was of prime concern to civilian health authorities, who feared that infected returning veterans might serve as foci for outbreaks of malaria, such outbreaks have failed to occur. This improvement in the malaria picture for the continental United States is due in part to active programs for control of anopheles mosquitoes and to the use of more modern suppressive and therapeutic antimalarial drugs. Indigenous cases of malaria have rarely been found in the northern part of the United States for over a decade.[10]

Rabies in wild animals has become a problem, particularly along the eastern seaboard. Prevalent in the fox and other small wild animals, this epizootic has resulted in increased numbers of cases in domestic animals and in several states among human beings. However, in Massachusetts, owing to an intensive program of vaccination of dogs carried out for a period of fifteen years under the auspices of local health departments and private veterinarians, rabies in domestic animals has not occurred since 1949, and a human case has not occurred since 1935.

In 1938 the first case of equine encephalomyelitis, eastern type, in men was recognized in Massachusetts, and a mosquito survey in 1939 indicated that mosquitoes were probably the vectors that carried the disease from birds to horses and to man.[11] Since that time viral encephalitides and other neurotropic virus infections have been recognized in increasingly large numbers, particularly in the southwest and Pacific areas. Effective immunization agents against these diseases for both animals and man are being developed. The discovery of DDT-resistant mosquitoes in a few cases has indicated the need for a continued search for new insecticides.

Environmental Health

Established originally for the control of communicable diseases, the environmental sanitation program has continually supervised public and private water supplies, and the proper disposal of human and industrial wastes. In most industrial states there has been an intensification of the program for the control of pollution of public water ways.[12] The incineration of garbage and refuse, or sanitary fill method, has become the accepted method of disposal of these domestic wastes.[13] Outbreaks of infectious vesicular exanthemas in hogs as well as the continued prevalence of trichinosis in human beings has emphasized the need for either not feeding garbage to hogs or cooking it before such feeding.[14]

Food sanitation has had to take into consideration the development of new methods of processing food, particularly rapid freezing.[15] The attempt to control food-borne diseases by periodic examination of food handlers has been generally abandoned.[16] Courses of instruction in proper methods of handling of food have proved to be a more effective measure.

The numerous developments in environmental health preclude mention of all of them in this presentation. However, among the more important is the increase in the percentage of milk pasteurization, the development of rapid high-temperature pasteurization and the in-place cleaning of pasteurization and other milk and frozen-dessert equipment.[17] In addition, many states have developed sanitary codes that apply to the proper sanitation in summer and recreational camps, swimming beaches, pools and other public facilities.[18]

Occupational Health

The dramatic Donora incident has brought about an intensification on the part of both public officials and industry in the control of the industrial pollution of the atmosphere.[19] Some of the largest cities have passed special regulations setting up standards for the discharge of substances into the atmosphere. State divisions of industrial hygiene have studied the tolerances of various chemicals inside as well as outside industrial establishments. For example, in 1944 in Massachusetts an outbreak of an unusual disease among workers in a plant manufacturing fluorescent bulbs brought about an investigation that uncovered beryllium poisoning as an occupational hazard.[20] More recently, the utilization of radioactive isotopes and apparatus generating radioactivity has necessitated the development of methods not only for safeguarding the workers in industry and in hospitals but also for the proper disposal of these substances. Massachusetts, among other states, has obtained the necessary equipment and has trained personnel to measure radioactivity in industrial wastes and in the conditions under which employees who use such substances may work. This same personnel and equipment are set up as the nuclei for civil-defense activities to determine the presence of radioactivity in case of atomic bombing. Periodic measurements of radioactivity in rain and river water are being taken in Massachusetts, particularly after tests are made in Nevada.

Maternal and Child Health

The passage of the Social Security Act in 1936 initiated in many states programs offering services for mothers and children. Increasing grants-in-aid

from the federal Government have been reflected in even greater appropriations for these services. Since the inception of the program in 1936, funds available for maternal and child health and for crippled children have nearly quadrupled. In 1936, the amount allotted by the Children's Bureau to the states was $6,650,000; in 1954 the recommended allotment to the states was over $24,000,000.

The yardsticks of maternal and infant mortality rates show that much has been accomplished in the past ten years in the field of maternal and child health. The maternal death rate per 10,000 live births in the United States decreased from 37.6 in 1940 to 7.2 in 1950. Infant mortality during the same period dropped from 47.4 to 29.1 per 1000 births.

The development of prenatal and postnatal educational programs urging expectant mothers to seek medical care early and to obtain proper follow-up study after delivery has continued. Many states are continuing with greater intensity the investigation of maternity deaths.[21] These investigations are usually carried out by consultants from the medical society in an effort to determine the cause of death in each case and to recommend steps for reducing maternal mortality. In Massachusetts there is not only a special maternal death committee of the state medical society, re-established in 1949, but also one that is studying neonatal deaths with a similar objective. Moreover, under the hospital licensing laws in Massachusetts each hospital is required to report promptly to the Department of Public Health each maternal death, thereby making such investigations prompt and effective.[22] The licensing program has also provided minimum standards for the equipment and operation of maternity units and nurseries for newborn infants. Special courses of instruction have been given for nursing personnel working in these units.

The prime cause of neonatal death is prematurity, and many state health departments with the cooperation of their medical societies and hospitals have started special programs for the care of premature infants. Special centers for premature infants have been set up in these states, and special provisions to transport such children have been made. In Massachusetts, in addition to these services, if the parents cannot afford hospitalization of these infants, the local board of health or the state health department has paid for such care since 1948.[23]

One of the major developments in maternal and child health has been the changing pattern in school health services. Formerly, an annual physical examination of each school child was the recommended school health program; now many states are utilizing a more thorough physical examination at spaced intervals of three or four years.[24] In many states such examinations are being made by the family physician. In fact school authorities and health departments have been encouraging parents to take their children to their family doctors for this service. The development of the Massachusetts vision test and the pure-tone-group audiometer has been responsible for improvements in the correction of vision and hearing defects in school children. These have become standard procedures in many schools in Massachusetts and many other states within the past ten years. Another development in school health programs is the requirement of periodic chest x-ray examinations of school personnel.[25] The purpose of this program is to protect the children from active cases of tuberculosis among the school personnel.

Services for crippled and handicapped children have continued to expand in most states as funds have been made available. Funds have increased nearly fourfold since the beginning of the program in 1936. In that year $2,850,000 was allotted to the states for services to crippled children. The recommended amount for the fiscal year 1954 was nearly $11,500,000.

Such patients are nearly always referred by the family physician on the basis of the inability of the parents to pay for the necessary care. The types of cases acceptable under the different crippled-children programs vary, but the scope has widened. In addition to the orthopedically crippled children some states accept deaf children, those with congenital heart disease, those with epilepsy and others. Crippled-children services include not only the provision of medical and surgical care but also hospitalization, physical therapy, speech therapy and the purchase of braces and other apparatus as indicated.[26] In Massachusetts the Lakeville State Sanatorium, which formerly admitted only patients with nonpulmonary tuberculosis started to admit patients with poliomyelitis in 1936, crippled children in 1949, patients with cerebral palsy in 1950 and arthritic patients in 1953.

A growing demand for child services in the United States, particularly for the physically and mentally handicapped, has been brought about in part by the rise in the birth rate from 15.1 in 1940 to 20.3 in 1950, an increase of about 35 per cent. The number of preschool children in 1953 is nearly 50 per cent higher, therefore, than the number in 1943. It is to be expected that this increase in the child population will be reflected in a continued demand for additional services from crippled-children and child-guidance clinics.

Dental Health

With the consideration that dentists were first employed in a state health department in 1918, that by 1933 only 12 states had dental public-health units, and that by July, 1951, all states but 2 had such units, the rapid strides made in dental health on a state level are impressive. On a local level, development and expansion have been no less rapid.[27]

These state and local programs were at first primarily concerned with education and the stimulation of the opening of dental clinics for school children by local authorities, but the most recent development has been the promotion of topical application of fluorides and the fluoridation of public water supplies. By April, 1953, 720 communities were adding fluorine to their public water supplies, serving a population of over 13,500,000.[28] It is expected that another 353 communities have authorized the addition of fluoride, and thus this preventive measure will soon be available to another 15,000,000 or more. Since over 3,000,000 are already drinking water that contains 0.7 to 2.0 parts per million of fluoride or more, a total of nearly 32,000,000 people in the United States are already or will soon be receiving the benefit of this measure, which prevents about 65 per cent of dental caries in children. Massachusetts, together with the rest of New England, has the highest rate of dental caries in the country. By April, 1953, 16 communities were already serving a population of 182,000 with fluoridated water, and 18 more with a population of 294,000 have authorized fluoridation, making the total population that will in future use fluoridated water supplies 476,000.

Local Health Services

The basic unit of any community program is the local health department. It is the responsibility of states not to give direct service but to encourage the development of local health departments, which may then give such direct service whenever possible. In 1940 only 50 per cent of the population was served by full-time local health departments. By 1950 this had increased to two thirds of the population, but one third of the population of the United States still continues to live in areas covered either by part-time health departments or by no health department.[29] In Massachusetts and the rest of New England the problem of full-time health departments is particularly difficult because of the town form of government. Elsewhere, in many parts of the country, counties or towns have united, forming joint or regional health departments that serve population groups of about 50,000 or more. In 1949 the Massachusetts Legislature passed an act requiring the formation of such regions or unions, unless a municipality having a population of less than 30,000 was able to demonstrate that it was giving adequate service.[30] In 1953 this act was amended, making such formations voluntary, but authorization for state assistance for capital outlay not to exceed 50¢ per person to local health departments was inserted into the bill.[31] In over 40 of the states such financial assistance from state appropriations to local health departments is now available, although in many of them the amounts are small. In New York state in 1943 a program was established whereby local health departments were assisted to the extent of $75,000 of the first $100,000 of their expenditures and $50,000 of each $100,000 thereafter.[32] Attempts to obtain federal legislation to assist local health departments financially with grants-in-aid administered on the federal level by the Public Health Service and on the state level by the state health departments have failed primarily because of the difference in the definition of public health.

Hospital Survey and Construction

With the passage of Public Law 725 of the 79th Congress the Hospital Survey and Construction Act provided a federal appropriation of $75,000,000 annually for the assistance in the construction of hospitals and health centers. Allotted in accordance with a formula provided by the law that was based on existing facilities and financial status, a grand total of $542,500,000 was appropriated by Congress, of which Massachusetts received $11,400,000. In Massachusetts this program has made possible an additional 2386 beds and 2 health centers.

Chronic Diseases

As the ratio of old people continues to increase, more and more emphasis will have to be placed on programs for the control of chronic disease and

Table 5. *Ten Leading Causes of Death, United States and Massachusetts, 1951.*

Cause	United States*		Massachusetts†	
	No. of deaths	Mortality *per 100,000*	No. of deaths	Mortality *per 100,000*
Heart disease	545,747	355.7	22,915	483.7
Cancer	219,239	142.9	8,666	182.9
Vascular lesions, involving central nervous system	162,949	106.2	5,660	119.5
Accidents (all kinds)	96,089	62.6	2,553	53.9
Certain diseases of early infancy	63,807	41.6	1,426	30.1
Influenza and pneumonia	48,428	31.6	1,356	28.6
General arteriosclerosis	32,065	20.9	1,325	28.0
Tuberculosis (all forms)	29,492	19.2	895	18.9
Chronic and unspecified nephritis	26,524	17.3	728	15.4
Diabetes	25,285	16.5	1,060	22.4
All causes	1,486,000	968.6	52,940	1,117.5

*Population of United States, 153,420,000. Source of data, Current Mortality Analysis 1951 Annual Summary, Federal Security Agency, Public Health Service National Office of Vital Statistics, October 15, 1952, Washington, D. C.

†Population of Massachusetts, 4,737,238. Source of data, Secretary of State of the Commonwealth, 1951.

programs providing normal living for the aged citizen, such as housing, recreation and opportunities for employment.

A review of the ten leading causes of death in the United States for 1951 reveals that chronic diseases such as heart disease and cancer account for more than 50 per cent of the total from all causes. In some states, like Massachusetts, there is an even higher proportion of persons above sixty-five years of age — for example, in 1950, 9.6 per cent of the population was sixty-five years of age or over in Massachusetts, as compared to 8.2 per cent in the United States. The problem of chronic disease in such states is thus even greater than in the "younger" states (Table 5).

The first public-health cancer program was started in Massachusetts in 1926. Since then many states have established similar programs designed to bring persons with suspected cancer into the doctor's office as soon as possible, to make the general practitioner aware of the possibility of the presence of cancer, and to furnish him with the necessary armamentaria to diagnose cancer in its earlier stages. The Public Health Service pioneered also in Massachusetts, in developing screening programs for heart disease in Newton in 1948[33] and began in that year in Framingham a long-term study to determine what types of persons are likely to have heart diseases later in life. A screening procedure — namely a one-lead electrocardiogram — has been developed as a result of the findings in Framingham.[34] Similarly, the Public Health Service pioneered in the study of diabetes as a public-health problem with a survey in Oxford, Massachusetts, in 1946 to determine the prevalence of unrecognized diabetes in the general population.[35] These studies are continuing over a period of years to calculate the development of diabetes in a known sample of the general population. The Massachusetts Department of Public Health, in 1950, attempted to evaluate self-testing of the urine for the presence of sugar as a screening device for diabetes in Gloucester,[36] having, in the previous year, initiated a program of multiple screening of the apparently well person for the presence of several chronic diseases.[37,38]

Similar multiple screening programs have been begun in many areas of the country with the prime objective of referring persons with suspected defects to their family physicians for final diagnosis and treatment.[39] The numbers of people who have been referred to the private practitioner can now be measured in the hundreds of thousands. Such programs have been carried out in Richmond, Virginia; in Atlanta, Georgia; in Alabama; in Indiana; and in San Jose and San Francisco, California.[40,41]

Throughout the United States the medical profession, social agencies, and health departments are becoming more conscious of the problems of the aging population and of the need of providing these people with a compatible environment in which to spend their declining years. Programs for the elderly and for the chronically ill are not the sole province of the medical society or the health department, but an integrated regional plan in which all agencies participate must be developed.

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MEDICAL PROGRESS

FUNCTIONAL DISORDERS OF MENSTRUATION IN ADOLESCENCE*

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THE purpose of this report is to review certain of the physiologic data that have been found of value in understanding and treating the functional disorders of menstruation in adolescent girls. Additional general information concerning this subject has recently been set forth elsewhere.[1,2]

MENSTRUAL AND REPRODUCTIVE PERFORMANCE OF THE ADOLESCENT GIRL

So common is erratic menstruation in the years immediately after the menarche that disturbances of menstrual function approach the status of a normal adolescent characteristic. There are, to be sure, cases in which a menstrual disorder connotes the presence of significant reproductive or constitutional disease. However, in most cases the disturbance is but a transitory reminder of the inherent complexity of the process of sexual maturation.

Establishment of norms of adolescent menstrual behavior thus becomes an essentially statistical task. Although comparatively few in number, the studies available for the definition of these norms are in good agreement. Boas,[3] for example, found the mean average age at the menarche to be 13.1 years, and the range 10 to 17 years in 236 non-Hebrew students at the Horace Mann School; Engle and Shelesnyak[4] obtained a mean menarcheal age of 13.5 years and a range of 11.0 to 16.3 years in 250 inmates of a Hebrew orphan asylum. For the past several generations daughters have tended to menstruate earlier than their mothers,[5] establishing a trend of obscure causation and significance. Since the time of onset of sexual function appears to be more closely related to the stage of physical development than to chronologic age, Mills[6] has suggested that the trend may be linked in some way with the gradual increase in adult stature that has been occurring in recent centuries.

Genetic factors are clearly of importance in determining the age of onset of the menses. The menarcheal ages of mothers and daughters are positively correlated, and the difference between the age of menarche in sisters is less than that of unrelated groups.[7] Broad-built, stocky girls tend to menstruate earlier than slender-built girls.[8] Climatic factors exert a detectable influence upon menarcheal age; menstruation begins earlier in central temperate than in cold northern or warm southern climates.[9]

The length of the menstrual cycle in the adolescent girl is extremely variable. In a study of 3140 menstrual cycles in 100 girls, Engle and Shelesnyak[4] found a range of 7 to 256 days and a mean of 33.9 ± 14.28 days. Although the most commonly recurring interval is 28 days, this value was modal in only 8 of the 100 cases. The variability of cycle length decreases as the elapsed number of cycles increases, being greater in girls who have experienced 20 to 24 menstrual cycles than in those who have experienced 25 to 29 cycles, and declining steadily with increasing elapsed time since the menarche. By the time 40 cycles have been experienced, the variability is comparable with that of maturity. The irregularity of the menstrual cycle is not correlated with age at menarche: "menstrual experience" is clearly of greater importance in establishing a trend toward regularity than the chronologic age of the girl at the time of the first menstrual period.

Although long intervals (periods of "temporary amenorrhea") are recorded by Engle and Shelesnyak during all seasons of the year, it appears that their occurrence is not altogether random. Long intervals initiated by a menstrual period in July are more than twice as numerous as those occurring in any other month. The fact that summer is the season during which the menarche occurs the least frequently is

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probably not unrelated; in all likelihood the two phenomena reflect the influence of the same factors. No studies concerning the duration of flow in adolescents are known to have been published. However, as any physician dealing with pubertal girls can testify, adolescent menstrual performance is also extremely variable in this respect.

These data have clinical utility in that they provide some indication of the limits of normal menarcheal age. From the nature of contemporary distribution curves it appears that persons who menstruate before the age of 10 or who remain amenorrheic after the age of 17 should be subjected to careful study. The genetic factor in menarcheal age can also be applied to clinical advantage: other things being equal, delayed menarche in the daughter of a late-menstruating mother need occasion less concern than delay in a girl whose mother began to menstruate at a comparatively early age. Summer amenorrhea need cause no alarm in girls whose menstrual function falls within adolescent norms in other respects. Judicious utilization of these facts can spare mothers and daughters much unnecessary anxiety.

These data are also of interest from the developmental point of view. They constitute circumstantial evidence for the presumption that the first menstrual period, though a dramatic occurrence, is only one event in the sequence that culminates in sexual maturity. Just as the menarche is normally preceded by a period during which budding of the breasts, appearance of an acid vaginal secretion containing cornified epithelial cells, and growth of axillary and pubic hair indicate the beginning of sexual maturation,[10-13] the menarche is followed by a period of erratic menstrual performance during which sexual maturation is completed. Only rarely does reproduction take place during this period of "adolescent sterility," as Ashley-Montagu[14] has called it. Particularly valuable data concerning the reproductive capacities of the adolescent girl have been accumulated by anthropologists. Malinowski,[15] for example, observed that the female inhabitants of the Trobriand Islands almost never conceive in their early youth in spite of unrestricted sexual congress.

In girls who do become pregnant in the immediately postmenarcheal years there is a high incidence of major maternal complications. Marchetti and Menaker[16] reported an incidence of 33.3 per cent of such complications in a study of 634 young mothers 16 years of age or younger. The toxemias accounted for the largest percentage, the rate being 19.7 per cent. Eclampsia occurred seven times and pre-eclampsia two and a half times as frequently in the adolescent group as in the obstetric population as a whole. Moreover, the younger the patient, the higher the incidence of toxemia. That such findings are by no means peculiar to the human species is clear from the studies of Mirskaia and Crew,[17] who observed a maternal mortality rate of 29 per cent in adolescent mice that became pregnant after their first mating. It appears that the immature organism is ill adapted to carry a pregnancy to term; its infertility can be interpreted teleologically as a protective mechanism.

Physiology of Sexual Maturation

As stated above, the disturbances of menstrual and reproductive function exhibited by the adolescent organism are but an outward manifestation of the complexity of the process of sexual maturation. Concerning the intimate details of this process, knowledge is profoundly incomplete. It appears that oogenesis, organization of the granulosa and theca interna, and growth up to the formation of the follicular antrum can proceed in the absence of the pituitary gland. However, for maturation of the follicle, ovulation, corpus-luteum formation and the elaboration of the follicular and luteal hormones, stimulation by the pituitary gonadotropic hormones is required.[18]

Pituitary Activation

By means of implantation experiments it is possible to demonstrate the presence of gonadotropic hormones in the hypophysis of certain species even in fetal life.[19] On a weight basis, the pituitary gland of the immature rat is as potent in gonadotropin as that of the adult rat.[20] From the meager data available it appears that the gonadotropin content of the human pituitary gland is comparatively low in childhood and that it undergoes a gradual increase with age.[21, 22] Gonadotropic hormones first become demonstrable in the urine of girls at about the age of 11[23]; as maturation proceeds, there is an increase both in the amount of gonadotropin and in the frequency with which it can be detected in the urine.[24]

In the adult animal ovarian function is under the direct control of the anterior lobe of the pituitary gland, and the active agents involved are thought to be three in number: follicle-stimulating hormone (FSH), luteinizing hormone (LH) and luteotropin (LTH). The female sexual cycle reflects the periodic release of these hormones from the pituitary gland in the proper sequence and amounts, a process upon which the estrogenic and progestational hormones are believed to exert an important reciprocal effect.

From the indirect evidence available, it appears that the hypophysis of the female differs fundamentally from that of the male in its mode of function. If ovaries be grafted into the anterior chamber of the eyes of rats castrated during adulthood, those implanted into females advance to corpus-luteum formation, whereas those implanted into males achieve merely follicular growth.[25] Only if injections of chorionic gonadotropin were given could ovulation and corpus-luteum formation be induced in the ovaries implanted into males. What

is apparently required of the male pituitary gland is that it secrete the gonadotropic hormones at a low and relatively constant rate; what is required of the female pituitary gland is a rhythmic discharge of larger amounts of gonadotropins at certain critical phases of the cycle and smaller maintenance quantities of gonadotropins in the interim phases. Accordingly, an important physiologic task of the adolescent female is the achievement of pituitary rhythmicity.

The manner in which the female pituitary gland acquires rhythmicity is quite obscure although certain data obtained from experiments on rats suggest that hormonal, rather than genetic, factors are of primary importance. Pfeiffer[26-28] has demonstrated that in both males and females castrated at birth the hypophysis remains bipotential until puberty and that it is capable of being differentiated into either the male or the female type, depending upon whether a testis or an ovary is present. Transplantation of testes into the newborn castrate female or even into the newborn intact female rat causes permanent differentiation of the hypophysis into the male type, with a low and relatively constant rate of secretion of the gonadotropic hormones. Under the influence of a masculinized hypophysis, a female rat remains in constant estrus; the ovaries are never maximally stimulated, and ovulation fails to occur. That the human hypophysis may be less vulnerable to androgenic influences than that of the rat is indicated by the rapidity with which cortisone treatment establishes sexual rhythmicity in girls with virilism due to congenital adrenal hyperplasia. However, the existence of large numbers of adult women with reproductive disorders resembling constant estrus suggests that Pfeiffer's observations may prove ultimately to have applicability to human hypophyseal function.

Tissue Responsiveness

Besides the factor of pituitary activation, that of the sensitivity of the reproductive tissues to hormonal stimulation is of fundamental importance in sexual maturation. The latter factor comprises the responsiveness of the ovary to gonadotropic stimulation and of the secondary sexual organs to the ovarian hormones.

That ovarian sensitivity to gonadotropic stimulation is, at least in part, a function of age has been demonstrated in a number of experiments on lower mammals. Corey[29] observed that injection of macerated whole pituitary glands into albino rats had no effect during prenatal life and no effect during neonatal life until the tenth to the fifteenth day. Wiesner[30] reported that doses of highly purified preparations of gonadotropic hormones, which produced estrus or even pseudopregnancy in rats 17-56 days old, had no perceptible effect on the ovary of the newborn rat. Pfeiffer and Hooker[31] found that the administration of pregnant mare's serum to mice from birth had no detectable effect on the ovary during the first 12 days of life. From the fifteenth until the thirty-fifth day only follicular growth and estrogen production, without ovulation, occurred. Appreciable luteinization was not observed before the thirty-fifth day of life. However, after this day superovulation and the formation of corpora lutea took place. Hertz and Hisaw[32] noted that in the female chinchilla rabbit a dose of pituitary extract that elicited a maximal ovarian response in the 12-13-week-old animal produced a feeble response in the 10-week-old animal and no detectable response in rabbits 4 weeks of age.

The occasional discovery of ripe graafian follicles in the ovary of the newborn and the infant[33] (one author, Runge,[34] has reported finding a corpus luteum in the ovary of a newborn infant) indicates that the immature human ovary is not totally refractory to gonadotropic stimulation. However, it seems probable that its threshold to gonadotropic stimulation is elevated. During the first six to eight years of life the number of growing follicles in the human ovary is small, but as puberty is approached the number increases.[33]

Age is clearly of importance in determining the response of the secondary sexual organs and other targets to estrogenic hormone as well. Wiesner[30] could not accelerate the differentiation of the rat uterus, which occurs during the first 14 days of life, by administering estrogenic hormone; reactivity to estrogen was found to develop gradually at a later stage. Selye and Albert[35] observed that estradiol in high doses not only fails to cause pituitary and adrenal hypertrophy in the immature rat but actually decreases the size of these organs. Wilson and Young[36, 37] found that large doses of estrogen were incapable of conditioning estrus behavior in 7-day-old guinea pigs but that by the thirtieth day the estrogen threshold was comparable to that of adult animals. The change in sensitivity appeared to be independent of ovarian action, since the response of animals spayed at birth and injected on the thirtieth day was no different from that of animals ovariectomized on the thirtieth day and injected 2 days later.

Allen et al.[38] demonstrated that large amounts of estrogen are required to induce withdrawal bleeding in the oöphorectomized immature monkey, whereas intermediate amounts will produce the same effect in the adolescent animal and comparatively small amounts are effective in the mature monkey. Gillman[39] reported that a dose of dihydroxy-estrone that produced minimal perineal swelling in the prepubertal baboon had pronounced effects upon the sexual skin of the adult animal. These observations are of clinical interest in that they suggest an explanation for the surprisingly large doses of estrogen often required to control functional bleeding in the adolescent girl.

Integration

Little is known concerning the process whereby pituitary gonadotropic activity, ovarian responsiveness and target-tissue sensitivity are integrated to achieve reproductive maturity. Presumably the anterior lobe of the pituitary gland initially secretes only enough FSH and LH to cause minimal growth of the ovarian follicles and the secretion of small amounts of estrogenic hormone. The secretion of gonadotropins is sporadic, and consequently the production of estrogen is also sporadic. The uterus and other target organs respond to these bursts of gonadotropin secretion with waves of growth and regression. Growth is cumulative, and after the passing of each wave the target organs remain slightly larger and better differentiated than before. The endometrium begins to exhibit proliferative phases paralleling the ovarian estrogen cycles and when the oscillations in the estrogen level become sufficiently pronounced to induce a vascular crisis in the endometrium the first menstrual period occurs. Finally, the rising peaks of estrogen production reach a level adequate to stimulate the release of a large quantity of LH from the pituitary gland. Ovulation takes place, initiating the luteal phase of the menstrual cycle. The endometrium, which proliferated under the influence of estrogen, is now subjected to the qualitatively different action of progesterone. Whether the endometrium and other target organs also "learn" to respond to progesterone in a step-like fashion is unknown. However, it seems probable that they do. Hartman[40] has coined the term "staircase phenomenon" to describe the step-like character of this process whereby the adolescent primate makes the transition from amenorrhea, through low and high grade nonovulatory cycles to the perfect ovulatory cycle.

Such meager evidence as has so far been accumulated from human studies is compatible with the foregoing hypothetical description of sexual maturation. The available data concerning the pattern of "total gonadotropin" excretion in adolescence have already been cited; it should be appreciated that although these data are roughly quantitative, they provide no qualitative information concerning the mode of secretion of the individual gonadotropic hormones. To them can be added the fact that the rate of estrogen secretion, which exhibits a slight rise in girls about the age of eight, has been shown to undergo a tremendous increase about the age of eleven, when excretion becomes cyclic.[23]

The available pathologic information can be summarized with the utmost brevity. The surface of the pubertal ovary has been observed to be strikingly smooth compared with that of the adult ovary, which is pitted and scarred as a consequence of repeated ovulation.[33] The ovaries of a twelve-year-old girl who died of a cerebral hemorrhage after having had four menstrual periods were found to contain only one corpus luteum, indicating that all but one of the periods must have been anovulatory.[41] The clinical history of adolescents suffering from dysmenorrhea suggests that these pathological observations, though fragmentary, may have general applicability. It is not uncommon for an adolescent girl who has had no pain with her earlier periods to develop dysmenorrhea suddenly a year or two after the menarche. Since there is good evidence[42] that cramps are related in some way to the prior occurrence of ovulation (except when associated with the passage of clots) their appearance probably signalizes a transition to more mature ovarian function.

Menstrual and Reproductive Performance of the Adolescent Monkey

Fortunately, there are excellent reasons for the belief that knowledge gained from studies of the sexual cycle of the infrahuman primates is applicable to man.[43] Of the various primates, those which have been studied most intensively are the rhesus monkey, the chimpanzee and the baboon. A great advantage in the study of these animals is the possibility of achieving satisfactory control of conditions and observations, and of employing a variety of objective methods.

Among the technics that have been utilized in the study of adolescence in the infrahuman primate are the following: cytologic study of vaginal smears and of sediment obtained by vaginal lavage; observations of the external sexual-skin cycle; controlled matings; direct inspection of the ovaries at different times of the cycle; histologic examination of ovaries biopsied or excised at known times of the cycle, or removed from animals that died on known menstrual dates; and rectal bimanual palpation of the ovaries throughout the cycle. The last-named method, which was developed by Hartman,[44] has proved remarkably informative. Although only gross ovarian changes can be made out in women, fine changes are detectable in the macaque, whose ovaries are readily accessible to the palpating finger and in which the follicle, when ripe, may comprise a large proportion (over half) of the total volume of the ovary. In favorable cases, therefore, ovulatory collapse of the follicle can be recognized with virtual certainty.

Macaque

Hartman's[40] classic monograph concerning reproduction in the *Macacus rhesus* monkey includes valuable data on the menstrual vagaries of adolescence. The Carnegie colony contained 15 females whose every menstrual cycle from the very first was observed. The initial cycles of these monkeys were irregular, and the flow was often abnormally frequent and profuse. As in the adolescent girl, amenorrhea was common in summer, which was demonstrated to be a nonovulatory, nonbreeding

season. The average body weight at first menses was 3350 gm. Although most of the animals were mated soon after puberty the lowest weight at the time of first conception was 4370 gm., the average being 5000 gm. This difference in weight indicates that general somatic maturation, as well as genital maturation, may well be essential for a complete reproductive potential.

Smith and Rubenstein[45] have supplemented these observations by means of a study especially directed toward the description of the menarche and the earliest ovulations in the adolescent macaque. As in Hartman's animals, the menstrual periods were very irregular, the mean cycle length over the nine-month period of observation being 30.6 ± 11.8 days. Rectal palpation of the ovaries, performed six days a week, revealed that the first menstrual cycles were unfailingly anovulatory. This finding was corroborated by the analysis of daily vaginal smears, which showed no aggregation or folding of the cells indicative of luteinization during the initial cycles. The length of the period of sterility after the menarche differed for the individual monkeys but in only 2 did it approach a year, the figure estimated by Hartman. Four ovulations and 4 conceptions followed brief periods of sterility in the 6 adolescent animals studied. Although in every case the initial ovulation resulted in conception, 3 out of the 4 conceptions resulted in spontaneous abortion. It appeared, therefore, that the animals were too immature to reproduce although their immaturity was not expressed in failure of ovulation. That sterility in the adolescent is a relative phenomenon dependent for its duration upon the tempo of the growth processes throughout the body and on general health was suggested by the ability of one animal, which conceived a month after the menarche, to carry a normal fetus to term.

Corner[46] has reported the results of autopsies on 6 macaques that had been menstruating for a year or less. None of the animals' ovaries showed signs of recent ovulation; 2 contained no corpora lutea, and 4 contained only old or atrophic corpora lutea.

Chimpanzee and Baboon

The external sexual-skin cycle of the chimpanzee and baboon enables certain phases of the menstrual cycle to be studied separately in a way not possible in the macaque or in man. In brief, the cycle is divisible into four phases of genital reaction: a preswelling phase or short interval period of ovarian follicular inactivity, a genital swelling phase corresponding in general to the follicular phase, a postswelling phase corresponding closely to the luteal phase and menstruation.

In the adolescent chimpanzee, striking changes occurred in the phases of the sexual-skin cycle.[47] As maturation proceeded, the preswelling and swelling phases and menstruation became shorter, and the postswelling phase became longer. The mean length of the cycle was 50 ± 4.38 days during the first months and 35 ± 0.79 during the second half of the seventh year after the menarche. The period of adolescent sterility varied from about four months to more than two years; the mean length was estimated to be one to one and a half years. There was a close correlation between the time of first conception and the appearance of shorter preswelling and swelling phases and longer postswelling phases. Although early abortions were frequent, fertile matings occurred, and corpora lutea were observed in the ovaries of animals still exhibiting a short postswelling phase. It appeared, therefore, that ovulation could occur during at least part of the period of short postswelling phases. The authors conclude that in the chimpanzee ovulation occurs during part of adolescence and that the relative sterility of the period is due to a deficiency of luteal function, the secretion of progesterone being insufficient to cause rapid detumescence of the perineum or to support pregnancy. It is suggested that the apparent deficiency of progesterone may be due to one of two circumstances. The hormone may be circulating in adult concentrations but may be relatively ineffective owing to the need for the same step-like preparation of the target tissues that Hartman has postulated for estrogen. Alternatively, the corpora lutea may secrete only small amounts of progesterone because of temporary inadequacy in pituitary secretion of LTH.

While the baboon is passing through puberty, the length and character of the component parts of the sexual-skin cycle are erratic, and only after some months or even years do the cycles become regular.[48] Menstrual bleeding is more profuse and prolonged than in mature animals. "Psychogenic" amenorrhea is common in newly captured baboons; there is complete resorption of the sexual skin, and at laparotomy the ovaries are shrunken and contain only atretic follicles. Housing the newcomer with one of the old inmates of the colony results in shortening the period of amenorrhea — an observation reminiscent of that seen in college freshmen and in teen-age girls entering nurse's training.

The most important clinical corollary of these facts is the need for the adoption of a lenient view toward menstrual irregularities in the adolescent girl and for exercise of the utmost restraint in the use of endocrine therapy. It is essential that the pubertal organism be given an adequate opportunity to achieve stability without meddlesome interference.

Clinical Disorders of Menstruation

No data concerning the incidence of adolescent amenorrhea or menorrhagia are available, since it is difficult to formulate an adequate definition, even, of what constitutes pathologic menstruation in this age group. A diagnosis of postmenarcheal amenorrhea is probably unwarranted unless there

is an interval of twelve months or more between periods during the first two years. Bleeding should probably be regarded as pathologic only if it produces dizziness, palpitation or weakness, lowers the hemoglobin content of the blood or lasts more than about seven days.

In a few adolescents with bleeding or postmenarcheal amenorrhea the clinical history suggests that sickness or strain may have contributed to sexual regression, an association of events noted frequently by Hartman[40] in the macaque. Mention has already been made of the greater frequency of amenorrhea in the summer: in view of the fact that functional bleeding and amenorrhea represent but different degrees of sexual hypofunction it is not surprising that episodes of functional bleeding also begin more commonly in the summer than in winter.[49]

The data that have been reviewed suggest that both postmenarcheal amenorrhea and bleeding result from failure of the organism to make a steady ascent of Hartman's staircase toward sexual maturity. Instead, after achieving some measure of ovarian-hypophyseal reciprocity, the organism regresses to a level at which pituitary stimulation or ovarian response or both are feeble and fitful. Crops of follicles start to mature, but do so sluggishly and fail to undergo the mid-cycle spurt of growth that culminates in ovulation and corpus-luteum formation. Rather, they undergo atresia and eventual replacement by a new crop of follicles. The level of circulating estrogen is abnormally low, and instead of undergoing strong rhythmic variations it teeters up and down. When the level of estrogen declines sufficiently the endometrium regresses and undergoes surface necrosis; full-scale desquamation of the endometrium does not occur.

Correspondingly, it is noted that if serial vaginal smears are taken from an adolescent with amenorrhea they may remain persistently atrophic in character, or they may exhibit cyclic changes in the proportion of cornified and noncornified cells. Persons with smears of the former type are "very amenorrheic," according to Browne's[50] terminology. Their prognosis is less favorable than that of girls whose smears fall in the latter group: these are "just amenorrheic," and in them there is periodic ovarian activity that falls short of producing overt menstruation.[51] Similar cytologic findings have been observed in adolescents with functional bleeding. If the endometrium is curetted to terminate such bleeding it may be either proliferative or atrophic; in the adolescent period one is particularly likely to encounter bleeding from an atrophic endometrium, as Hamblen[52] has pointed out.

Although it is uncertain to what extent steroid substitution therapy is indicated in postmenarcheal amenorrhea of the functional type, there can be no question concerning the necessity for its use in functional bleeding, a disorder that may require urgent treatment. Though fatal hemorrhage is rare,[53] debilitating anemia is not uncommon. Sound treatment of functional bleeding is predicated upon the closest possible imitation of nature. In this connection the vaginal smear has real clinical utility, as pointed out by Rubenstein.[54] More easily obtained than an endometrial biopsy, the smear gives an indication of the degree of ovarian hypofunction and, as a corollary, of the type of substitution therapy required. If estrogen secretion is reasonably adequate, as attested by a well cornified vaginal smear, the administration of progesterone at intervals of four to six weeks is often the only treatment necessary. If the rate of estrogen secretion is low, as indicated by a poorly cornified vaginal smear, bleeding may be more difficult to control. In such cases, cyclic progesterone therapy may fail completely, since prior estrogenic priming has been inadequate. Even curettage may arrest the bleeding only momentarily, because estrogen-stimulated endometrial growth is essential for hemostasis. However, if the normal physiologic sequence of estrogen followed by estrogen and progesterone is imitated therapeutically, the clinical response is excellent.

To what extent the beneficial effects of these steroids are due to their conditioning effect upon the reproductive tissues, whose sensitivity to endogenous estrogen and progesterone they presumably increase, and to what extent their beneficial effect is wrought through pituitary or other mechanisms is unknown. It may be that by the induction of periodic menstrual desquamation in as physiologic a manner as possible the adolescent is merely "tided over" until mature pituitary rhythmicity is achieved as a result of the passage of time. On the other hand, if the thesis of the Smiths[55] is correct (that is, that the breakdown products of a secretory endometrium act as a stimulus to pituitary secretion, whereas those of a proliferative endometrium do not) periodic transformation of the endometrium to the secretory form may accelerate pituitary maturation.

Follow-up data concerning the subsequent menstrual and reproductive performance of adolescents who have suffered from pronounced functional irregularities are meager. Klingelhöfer[56] reported that of 12 patients who received conservative treatment for functional bleeding, only 3 had menstrual disturbances subsequently, and only 2 failed to become pregnant.

It is evident that the available knowledge regarding adolescent reproductive physiology is distinctly superficial, despite the enormous effort that has already been expended in its accumulation. Even in the monkey, concerning whose sexual cycle information is remarkably precise and reliable, virtually nothing is known about basic controlling mechanisms. The field itself is in its adolescence.

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MEDICAL INTELLIGENCE

ANAPHYLACTOID REACTION TO THE HYDRIODIDE OF DIETHYLAMINOETHYL ESTER OF PENICILLIN G (NEO-PENIL)

Report of a Case

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JENSEN, Dragsted and Kiaer,[1] in the course of their investigations, found a new penicillin, which in addition to its prolonged antibacterial effect, produced sputum and lung-tissue concentrations several times greater than those achieved with similar doses of sodium or procaine penicillin. Most of the problems encountered with penicillin sensitivity have been discussed by Peck and his associates.[2] Severe reactions have been described by Cormia et al.,[3] Wilensky[4] and O'Donovan and Klorfajn.[5] Waldbott[6] reported a death that followed the intramuscular injection of penicillin, and Mayer and his co-workers[7] recently presented 6 cases of anaphylactic-like shock syndrome, with 1 death.

There have been a few reports of severe reactions with the hydriodide of diethylaminoethyl ester of penicillin G. Grigsby, Haight and Finland[8] found this type of penicillin better tolerated than other forms. Wylie-Smith[9] described a severe anaphylactic reaction, with unconsciousness and convulsions, that immediately followed the intramuscular injection of this antibiotic. Heathcote and Nassau[10] observed bronchospasm and syncope in others. The following case is presented to add to the present knowledge of reactions to this new type of penicillin.

CASE REPORT

D. H., a well developed and well nourished 44-year-old woman, who was seen on October 28, 1952, had been under treatment for allergic rhinitis and bronchial asthma for 2 years. She had been receiving hyposensitization with allergic extracts during this period, with a good measure of relief and without any untoward reactions. At the time she was seen, a slight cough, hoarseness, and nasal discharge, which appeared to be purulent, had developed. There was some rhinorrhea but no dyspnea.

Physical examination revealed a temperature of 99.4°F. The mucous membranes of the nose and throat were injected. The lungs were clear, and the heart sounds were normal. Examination of the blood showed a white-cell count of 14,500, with 76 per cent neutrophils, 16 per cent lymphocytes, 3 per cent monocytes and 5 per cent eosinophils. A roentgenogram of the chest demonstrated a moderate amount of increased hilar and peribronchial markings. The hoarseness had started 2 days previously. There was a record of penicillin having been received both intramuscularly and in aerosol solution on September 16, without any reaction.

It was decided to discontinue the weekly administration of allergenic extract, and at 6:30 p.m. on October 28, 500,000 units of the hydriodide suspended in 1.3 cc. of diluent was injected intramuscularly in the deltoid muscle of the left arm, care being taken to aspirate before injection to make certain that a vein had not been entered. Approximately 1 or 2 minutes later the patient complained of wanting to defecate and urinate. She was taken to the bathroom feeling faint and weak. In approximately 20 minutes, she was unconscious, a few convulsive movements of the arms and legs having developed. She voided involuntarily. The pulse was 150 per minute and feeble, respirations 44, and the blood pressure 64/24. The heart sounds were feeble and distant, and there were wheezes and sonorous and sibilant rales throughout both lung fields. Cyanosis was generalized; a red erythema was observed around the site of the injection of the left arm.

A tourniquet was immediately placed on the arm above the site of the injection, and 0.5 cc. of epinephrine hydrochloride, 1:1000 solution, was injected in the opposite arm. Oxygen was administered by B.L.B. mask, at a rate of 8 liters per minute, and the patient was placed in Trendelenburg position. The injection of epinephrine hydrochloride, 1:1000 solution, was repeated in 5 minutes when there was no apparent response. She was given diphenhydramine hydrochloride, 3 cc. intramuscularly, with a slight improvement. After repeated injections of epinephrine hydrochloride, she improved enough to be transferred to the hospital. Continuous oxygen was administered, since she continued to be dyspneic and cyanotic. The face, lips and ears were red, covered with sweat and slightly swollen. There were still a few wheezes in her lungs, but the breath sounds were distant. In the hospital emergency room, she continued to have difficulty in breathing. A No. 16 F catheter was passed through the nose and into the trachea at the first deep inspiratory movement. This resulted in increased difficulty in respiration and violent coughing, with the production of thick, tenacious mucus. The catheter was attached to an electric suction pump, but before any secretions were obtained, the coughing became severe and the patient struggled considerably. The catheter was removed, and in about 3 minutes, she regained consciousness, the pulse became full, and respirations became normal. She had responded completely 3½ hours after the injection. She remained in the hospital overnight and was discharged on the next day, having spent an uneventful and restful night.

Five days later she was re-examined, and hyposensitization with house-dust extracts and mountain cedar was resumed without untoward effect.

DISCUSSION

In this allergic patient who had received sodium and procaine penicillin by the intramuscular and aerosol routes and had never had any abnormal mild or severe reactions, a severe reaction to the hydriodide of diethylaminoethyl ester of penicillin G developed. She had taken iodides previously without any unusual dermatologic or gastrointestinal reactions. She gave a history of having had a severe episode of ivy poisoning and urticaria in the past.

This reaction was relieved considerably, with the exception of the bronchospasm, by the series of injections of epinephrine hydrochloride. The passage of the tracheal catheter, as suggested by Cardon,[11] resulted in complete recovery.

SUMMARY

A case of anaphylactoid shock due to the hydriodide of diethylaminoethyl ester of penicillin G is reported in a patient who had had no previous reactions, either mild or severe, with sodium or procaine penicillin. The abrupt termination of acute,

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persistent bronchospasm was observed on the introduction of a catheter into the trachea.

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BY THE LONDON POST

Cost of Prescribing—Medical Responsibility—Men and Mountains

John Lister, M.D.

London, England

THE latest and most constructive approach to the problem of stabilizing the cost of the National Health Service has been the appointment of the Guillebaud Committee. Under the chairmanship of the Cambridge economist, Mr. C. W. Guillebaud, the Committee will review the present and prospective cost of the service and will "suggest means of ensuring the most efficient use of such Exchequer funds as may be available and advise how, in view of the burdens on the Exchequer, a rising charge upon it can be avoided, while providing for the maintenance of an adequate service." The appointment of this committee has been attacked by the Opposition with vehemence. Mr. Bevan accused the Minister of Health of seeking to mutilate the service and argued that in fields of expenditure such as the dental and ophthalmic services, where the initiative lay with the patient, the demand had declined although on the pharmaceutical side, where the initiative lay mainly with the doctors, it had increased. He suggested that the answer was not to penalize the patient but to make investigations into the profits of the large drug houses and stiffen the discipline over the general practitioner's prescriptions. Such control over medical practice was, of course, forecast by the gloomy prophets before the National Health Service started, and although any rigid control over prescribing would be resisted by the medical profession, the wholesale use of expensive proprietary preparations cannot be defended, especially when their therapeutic value is often not superior to that of equivalent standard pharmacopeal preparations. In response to these attacks and under Treasury pressure the pharmaceutical industry has itself embarked upon a price investigation. The *Times*, calling attention to this, warned that such investigations are a classic approach to control. It also urged that when a critical eye is cast on British pharmaceutical prices, the conditions that seem to account for the present success of the American industry should be noted. It recalled the American industry's claim that three quarters of present sales are of products introduced in the last ten years and the observation of an Anglo-American productivity team of 1951 that this has resulted from an "intensely competitive" research and development effort. It was pointed out that although when costs and prices are investigated there is a temptation to cut margins for the sake of appearance, this should not be done at the expense of research. It should be remembered that much research yields no return and that it is not always possible to attribute the cost of any research project to the particular product emerging from it. Furthermore, so long as genuinely competitive conditions are established, no intervention in prices should be necessary and might indeed be against the public interest.

* * *

A matter that has recently caused great anxiety in the medical profession is the tremendous increase in the number of legal actions for negligence that patients are bringing against doctors and hospitals. The offices of the medical-defense societies have long lists of pending litigations, and doctors are trying to determine how far they can be held responsible for the unsuccessful outcome of a patient's treatment. With the ever-widening range of benefits offered to the citizen under the Welfare State he has become increasingly conscious of his rights — especially those regarding compensation. Furthermore, the provision of free legal aid, under the Legal Aid and Advice Act of 1949, for those who cannot afford to pay for it has opened the way for many more persons to go to court. Speaking about this at the annual meeting of the British Medical Association, the secretary of the Medical Defence Union, Dr. R. Forbes, said that there was an attitude abroad of "Let's have a go — we are not standing to lose anything if we can invoke legal aid."

Discussing the relations among the Law, the hospital and the doctor, the *British Medical Journal* has tried to answer two pertinent questions.* The first is whether doctors have become more negligent, and the second whether the National Health Service has altered the attitude of the public. Regarding

*Law, hospital and doctor. *Brit. M. J.* **1**:1378, 1953.

the first question it is pointed out that the medical profession has carried an increased burden of work since the Service started and that this in itself may carry an increased possibility of error. Furthermore, the advances in both medical and surgical science have in many cases increased the possible hazards of the available therapeutic measures, so that good judgment in their use has become more necessary than ever. Having admitted these points one must say that there has been a profound change in the attitude of the patient to the hospital. In former days there was a great sense of loyalty to the local hospital, for which the local public worked and helped raise funds. Now that it has become a State hospital the same people have come to think that if they are the subject of some mishap they should look to the hospital and the State for compensation. There is probably no wish on the part of the patient to victimize the doctor concerned, but as part of the State hospital he comes to be regarded as fair game. From the legal point of view, the question of responsibility is complex, but in a case in 1951 the judge expressed the opinion that the hospital was liable for the negligence of a doctor on its permanent staff. Alarmed at this judgment, the Ministry of Health has instructed hospital authorities to obtain from the doctor in question a part or all of the damages or costs awarded when the authority has been made responsible for the alleged negligence.

Although no physician would deny that the acceptance of responsibility is one of his main duties to his patient the present position is far from satisfactory, and it is not surprising that certain hospital appointments, particularly in casualty departments, are difficult to fill because young doctors are not prepared to run the risk of court action.

* * *

To conclude these notes in a less controversial tone, it is pleasant to recall the universal pleasure with which the news of the conquest of Everest was received on Coronation day. It seemed a happy chance that the news should arrive on that day, for the spirit of adventure and perseverance that had inspired all the unsuccessful attempts and finally made possible the present success seemed to be symbolic of the hope with which Great Britain entered on a new Elizabethan age. There is no doubt that medical science played a vital part in the expedition's success, and Colonel Hunt has paid tribute to the help he received from his medical staff. Careful acclimatization, adequate oxygen supplies, protective clothing and proper feeding were a few of the aspects of medical care that contributed to the good health of the party. It is worth remembering that when Mallory was asked why men attempted to scale such obstacles as Mount Everest — he replied "Because they are there." Perhaps doctors should remember that they will always have obstacles to overcome and that the problems discussed above are no doubt soluble — in time.

MASSACHUSETTS PHYSICIANS ART SOCIETY

18. In the Fenway (Muddy River and Sears Roebuck Building as they appeared in 1933)

Exhibited at Massachusetts Physicians Art Society, 1953

Pencil Sketch by

J. DELLINGER BARNEY, M.D.

Formerly, Chief, Genitourinary Service
Massachusetts General Hospital

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 39351

PRESENTATION OF CASE

A sixteen-year-old girl was admitted to the hospital because of two convulsive seizures.

The patient had been born normally at full term after an uneventful pregnancy, during which the mother had had no known illnesses. The patient had been cyanotic since birth. Seven hours after delivery, she reportedly had a generalized convulsion. Additional convulsions, which occurred at five weeks and three years of age, were characterized by generalized rigidity of the body followed by jerking movements of the arms and legs with escape of urine, and lasted about two and a half minutes. During infancy she gained weight slowly. She sat up at eighteen months, and at two and a half years stood poorly and walked only with help. At the age of four and a half years, during an attack of otitis media, she had a generalized convulsion followed by "coma" for two weeks, during which another convulsion occurred. She recovered without any residual neurologic disability. Between the ages of five and twelve and a half years, her case was extensively studied at another hospital. At the age of ten, she was given oxygen for two hours daily for about eight months, with a reported 20 per cent decrease in the hematocrit. Phlebotomy was advised, but refused. She continually had marked exertional dyspnea, but could climb stairs slowly and was able to do schoolwork with private instruction at home. She was left-handed. Two weeks before admission, immediately after bending over a basin and washing her hair, she suddenly felt "dizzy" and nauseated, her speech became "garbled," she felt her eyes roll up to the right, and she could not see. She improved rapidly to her previous state of health, although her vision remained blurred. Six days before admission, she had another short "dizzy spell," with increased impairment of vision. Phlebotomy, with removal of 500 cc. of blood was done at another hospital. While leaving the other hospital, she had another transitory attack of "dizziness" and blurred vision, in which she appeared pale. On the following day, she again had an episode of visual disturbance. On examination during a brief visit to the hospital three days later, she was cyanotic, with marked clubbing of the fingers and toes. The heart was enlarged, with a protodiastolic gallop. She was alert, but had a right homonymous field defect. The tendon reflexes were more active on the right than the left. The right plantar reflex was questionably extensor. The temperature was 99.8°F., the pulse 110, and the respirations 24. The hemoglobin was 21.5 gm. per 100 cc., and the white-cell count 6400. An electrocardiogram revealed right-ventricle strain. Fluoroscopy demonstrated a questionable hypertrophied left ventricle and abnormal markings of the great vessels. She refused to remain in the hospital for further investigations. About twenty hours before admission she had an unwitnessed convulsive seizure. Twelve hours later, she had a seizure in which the right leg suddenly extended, whereupon she attempted to say something; immediately there were clonic movements in the right leg, which spread to both arms and both sides of the face, and she became wholly unresponsive. Consciousness returned in about five minutes, after which she was drowsy for an hour.

Physical examination revealed a somewhat apprehensive, moderately cyanotic, small, undeveloped girl with rapid respirations but in no acute respiratory distress. A 2-mm. purplish raised lesion, which blanched on pressure, was noted in the skin of the left forearm. There was a 15° right dorsal scoliosis, with prominence of the right posterior part of the chest, that was less apparent in the prone position. The auditory canals, eardrums, nose and throat were normal. There was normal respiratory excursion of the chest. The lungs were clear. The left border of the heart was percussed 12 cm. from the midsternal line in the fourth and fifth left intercostal spaces. The point of maximum impulse was heaving over a 4-cm. area 12 to 13 cm. from the

midsternal line in the sixth intercostal space. The right border was not made out. There was a sinus arrhythmia. No murmurs were heard. A third heart sound in systole was heard loudest in the tricuspid area. The pulmonic second sound was normal in intensity except low along the left sternal border, where it was accentuated. There was no neck-vein distention. The nontender liver edge was felt 3 cm. below the right costal margin. The spleen, also nontender, was palpable 3 cm. below the left costal margin on deep inspiration. There was slight pretibial and ankle edema.

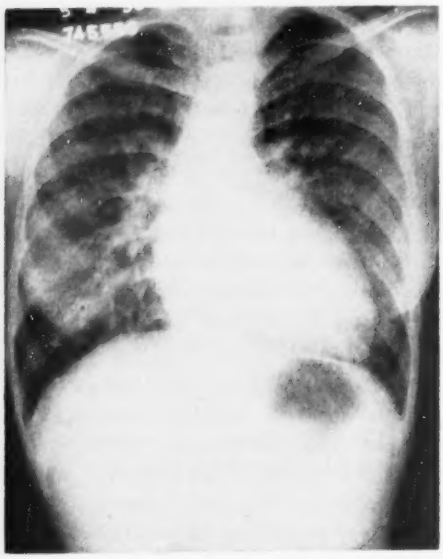

FIGURE 1. *Roentgenogram of the Chest Showing Marked Cardiac Enlargement and Engorgement of the Pulmonary Vessels.*

On neurologic examination the patient was alert and oriented, without any impairment in the use or understanding of speech. She could see large objects but could not read 10-mm. print. There was a complete right homonymous hemianopia. The disk margins were indistinct; retinal vessels were normal. The pupils were equal (5 mm.) and reacted briskly to light and on convergence. Ocular movements were normal. Hearing was good in both ears. The remainder of the cranial nerves were unremarkable. The gait was slightly unsteady, but there was no weakness or impaired co-ordination of the limbs. Tendon reflexes were sluggish and equal in the arms and active in the legs, and the right knee jerk was brisker than the left. The abdominal reflexes were active and equal. The plantar reflexes were normal bilaterally. There were no sensory changes.

The temperature was 99.2°F., the pulse 100, and the respirations 35. The blood pressure was 110 systolic, 70 diastolic.

The urinary sediment contained 2 to 8 white cells and occasional granular casts per high-power field; the urine was otherwise unremarkable. Examination of the blood showed a hemoglobin of 20.0 gm. per 100 cc. and a white-cell count of 11,400. A nose culture grew out only abundant *Neisseria catarrhalis*; five blood cultures were negative. On lumbar puncture, the spinal fluid was under a pressure equivalent to 90 mm. of water and was clear; it contained 2 fresh red cells per cubic millimeter and no white cells and 12 mg. of total protein and 100 mg. of sugar per 100 cc. There was no growth on culture. Roentgenograms of the chest demonstrated a scoliosis of the dorsal spine, with convexity to the right and related distortion of the ribs on either side. The heart was enlarged (Fig. 1) preponderantly in the region of the right ventricle, producing some rotation of the heart to the left (Fig. 2). The aortic arch appeared diminutive. The pulmonary arteries in the region of the hili were somewhat larger than normal, and their radicles were markedly distended in both lung fields. Although a "hilar dance" was noted fluoroscopically, it was not exaggerated. There was exaggeration of the lung markings throughout both lung

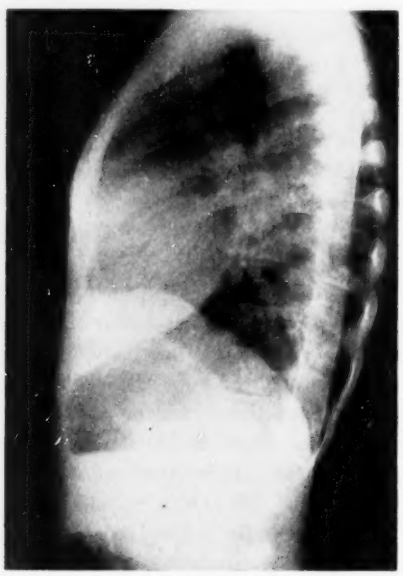

FIGURE 2. *Lateral Roentgenogram of the Chest. The enlarged right ventricle encroaches upon the retrosternal space.*

fields. The liver appeared slightly enlarged, and the spleen was definitely enlarged.

Phlebotomies were done on the first three hospital days, with removal of a total of 560 cc. of blood. On the third hospital day the patient complained of headache. Neurologic examination disclosed no new findings. She continued to have fever, the temperature ranging between 99.2 and 102°F. On the fourth hospital day, while straining at stool, she suddenly stopped breathing and momentarily lost consciousness. She responded immediately to artificial respiration. On examination she was conscious but disoriented. The pupils were dilated and equal, and there were wandering movements of the eyes. The neck and back were slightly stiff. The remainder of the neurologic findings were as before. Auscultation of the chest revealed a small patch of rales at the right base in the anterior axillary line. Lumbar puncture gave 6 cc. of grossly purulent spinal fluid, under a pressure equivalent to about 600 mm. of water, containing 51,000 white cells per cubic millimeter, 98 per cent of which were neutrophils. No organisms were seen on direct smear, but culture grew out alpha-hemolytic streptococci. A semiquantitative test showed no sugar; the protein was 540 mg. per 100 cc. A few hours later, the patient became restless and unco-operative, with short, deep respirations at 32 per minute and a pulse of 160. Shortly thereafter she suddenly became deeply unresponsive, reacting only with a blink or slight withdrawal to a loud noise or pinprick. The eyes moved conjugately from side to side. The pupils were 4 mm. and reacted to light. The disk margins were blurred, with engorgement of the veins. Other neurologic findings included weakness of the entire left side of the face, diminished pinprick sensation on the entire left side of the body, marked weakness of the left arm and slight weakness of the left leg. The tendon reflexes were sluggish and equal, and the left plantar reflex was questionably extensor. The neck was markedly stiff.

On the fourth hospital day an operation was performed.

Differential Diagnosis

Dr. Ralph A. Ross*: To summarize, this patient had congenital heart disease, with cyanosis noted at birth; repeated, isolated, nonlocalizing seizures, starting during the neonatal period; evidence of a lesion in the left cerebral hemisphere occurring two or three weeks before admission; and frank meningitis as the event that preceded operation. I shall try to make a single or a unified diagnosis that brings in all the factors given to me.

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To start with the diagnosis of congenital heart disease, what sort of congenital heart disease causes an enlarged heart, cyanosis at birth, polycythemia, clubbing and right-ventricle enlargement without extreme dyspnea and permits life up to the age of sixteen years? I also have to take into account the fact that no murmurs were heard at the time of the examination. That the pulmonic second sound occurred loudest low along the left sternal border suggests there may have been rotation of the great vessels, permitting the pulmonic second sound to be heard more easily in this position. The position of the third heart sound in the tricuspid area intrigues me because I wonder whether it was really a third sound or a murmur due to a defect of the atrial septum. There was evidence of heart failure with minimal edema, gallop rhythm and some enlargement of the liver. The x-ray films ought to be very helpful. May I see them?

Dr. Joseph Hanelin: This set of chest films, made on the day of admission to the hospital, shows the greatly enlarged heart (Fig. 1) and predominantly what appears to be enlargement of the right ventricle as indicated by encroachment of the heart upon the retrosternal space as seen in the lateral view (Fig. 2). The vessels in the lung fields are distinctly enlarged both at the lung roots and in the peripheral portions of the lungs. I think the statement that the aorta is diminutive might be questioned; we can see a reasonably good aortic outline with the aorta descending along the left side and a well defined aortic knob, certainly for a sixteen-year-old girl. The spleen is enlarged to some degree, and the liver may be slightly enlarged.

Dr. Ross: Can this picture be explained on the basis of the tetralogy of Fallot? I should think with full lung fields — evidence of good pulmonary circulation — that that is not a tenable diagnosis. Are there any other common diagnoses that fit in? I think mainly of complete transposition of the great vessels with a shunt between the two sides of the heart — a defect of the atrial septum or a patent ductus arteriosus permitting flow of some oxygenated blood into the peripheral blood stream. There were no murmurs; that in itself is not helpful in the diagnosis of this type of cyanotic heart disease. Taussig[1] states that she has seen several youngsters with complete transposition who have grown fairly well along in years with persistent cyanosis and with small basal heart shadows. Only once has she seen the post-mortem findings; in that case a defect of the atrial septum accounted for the fact that the patient was able to survive despite the transposition of the great vessels.

With the persistence of the cyanosis and a high hematocrit, there is a good possibility that thromboses occurred from increased viscosity of the blood and anoxia; therefore, frequent cerebral episodes

may well have taken place. I believe that is a satisfactory explanation for the scattered episodes of unconsciousness and seizures during the early part of the course. The otitis media, with the coma and convulsions, may well have been explained on the basis of the presence of the polycythemia aggravated by dehydration due to the fever and infection.

How can I explain the fever, splenomegaly and question of petechiae? Five blood cultures were taken, probably in rapid succession, during the two or three days the patient was in the hospital, all of which were negative. Do they rule out the possibility of subacute bacterial endocarditis on the basis of the congenital heart lesion? No, I should say. She may well have had septic emboli localizing in the thrombotic areas of the brain that had been there for some time. In support of that possibility I think the finding of alpha-hemolytic streptococcus as the cause of meningitis is helpful. I should suppose that the operation done was burr holes to evacuate the probable abscess. The terminal events leading to neurologic signs on the opposite side, I think, were due to the overwhelming meningitic response that followed the rupture of the abscess.

My diagnoses are congenital heart disease, cyanotic type, with complete transposition of the great vessels and with shunt and probably defect of the atrial septum; brain abscess, with rupture and meningitis, the abscess being in the left temporal area; and subacute bacterial endocarditis.

Dr. Robert H. Fennell, Jr.: Dr. Skinner, you saw this patient on the ward; would you tell us your opinion?

Dr. A. L. Skinner: Our impression on the ward about paralleled that of Dr. Ross; I can add little. We thought sepsis was present as Dr. Ross outlined in his final diagnosis.

Dr. Fennell: Dr. Talbert, would you discuss the neurologic picture?

Dr. Rhett Talbert: The neurologic findings were just as described. There was a complete homonymous hemianopia and a slight difference in patellar reflexes. The patient could stand on her feet but she was unsteady in walking. It was almost impossible to be certain about the visual acuity. This combination of neurologic findings pointed to a lesion in the left hemisphere. At that time the patient had a normal spinal fluid and at the time of admission a normal temperature; fever did develop later. Our impression was that she had a lesion in the left hemisphere probably thrombosis secondary to the polycythemia or, as a second possibility, bacterial endocarditis with embolic encephalomalacia as a complication of that. When we obtained the second spinal fluid, we realized that we had been mistaken in not recognizing earlier that she had an abscess that had now probably ruptured into the ventricle, with ventricular empyema as the terminal event.

Clinical Diagnoses

Congenital heart disease, with transposition of great vessels and septal defect.
Brain abscess, left occipital area.
Meningitis, secondary to rupture of brain abscess into ventricle.
Possible subacute bacterial endocarditis.

Dr. Ralph A. Ross's Diagnoses

Congenital heart disease: transposition of great vessels; defect of atrial septum.
Brain abscess, left temporal area, with rupture.
Subacute bacterial endocarditis.

Anatomical Diagnoses

Congenital heart disease: transposition of great vessels, defect of interventricular septum, patent foramen ovale, patent ductus arteriosus, and bicuspid pulmonic valve.
Brain abscess, left occipital lobe.
Meningitis, acute.

Pathological Discussion

Dr. Fennell: The operation that was performed was, as Dr. Ross predicted, the making of occipital burr holes. Perhaps Dr. Brendler will describe it.

Dr. Samuel Brendler: At operation two occipital burr holes were made. When a ventricular needle was inserted through the left burr hole and directed downward a structure that felt like a capsule or membrane was pierced at 3 cm. Aspiration then yielded approximately 10 cc. of thick, greenish-gray, foul-smelling, purulent material. A ventricular needle inserted into the right burr hole and directed upward and laterally yielded sanguinopurulent material at a depth of 4 cm.

Dr. Fennell: The patient did not regain consciousness and died several hours after the operative procedure.

At autopsy we observed the same findings that had been noted clinically: the patient was small and undeveloped, had clubbing of the fingers and was cyanotic. The principal findings were in the heart and great vessels. There was complete transposition of the great vessels. The aorta arose on the right side, and the pulmonary artery from the left side. All the branches came from the aorta in a normal fashion; the innominate, the carotid and the subclavian arteries arose and were distributed normally. The pulmonary artery branched normally, the right branch passing behind the aorta. There was a patent ductus arteriosus, which measured 3 mm. in diameter. The veins entered in a normal fashion, the venae cavae on the right and the pulmonary veins into the left atrium. The heart was large for a girl of this size, weighing 300 gm. The right ventricle was especially large and was dilated and hypertrophied to the degree that it nearly equaled the left ventricle; the wall measured 8 mm. as compared to the

12 mm. of the left ventricle. There was a high, large defect of the interventricular septum that measured 1.5 cm. in diameter, had a smooth rounded edge and gave no evidence of endocarditis. There was also a patent foramen ovale, which was small and was guarded. It was possible to probe it from the right side, but I doubt if blood flow could have occurred from the left to the right. The pulmonic valve was bicuspid but it had a perfectly smooth contour and gave no evidence of infection. The coronary arteries arose normally and were distributed normally.

With this type of malformation, the blood coming into the right atrium goes into the right ventricle and is ejected into the peripheral circulation and comes back in the same fashion. The blood entering the left atrium is ejected by the left ventricle and goes to the lungs, whence it re-enters the left atrium. Thus, if there is no communication between the two sides, there are two closed circuits, and this is incompatible with life. Three communications were present in the case under discussion, and mixing of the blood in the two circuits did occur; it was only by virtue of this mixing that life was at all possible (Fig. 3). The patient had a maximum opportunity as regards this point — all three openings were present. In the review that Hanlon and Blalock[2] presented in 1948 their tabulation of duration of life in patients with transposition and the various associated anomalies shows, however, that the most favorable combination of defects is a patent foramen ovale and a defect of the interventricular septum.

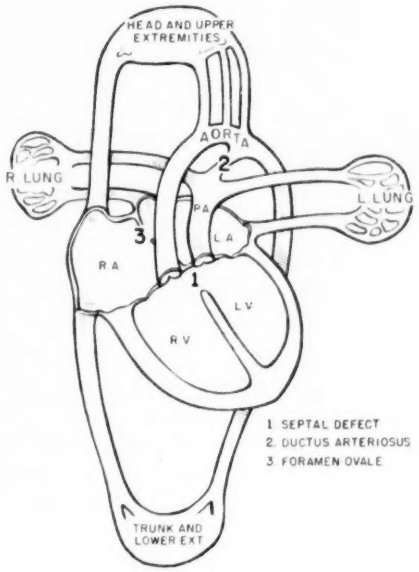

FIGURE 3.

There was no evidence of bacterial endocarditis in this case. We searched carefully for some focus of infection but were unable to find one. The rest of the findings in this case were not remarkable except those in the brain. The lungs showed fibrous intimal thickening of the arteries and arterioles to a moderate degree. The bronchial arteries were prominent grossly. The spleen was large, as noted clinically; there was no evidence of acute splenitis, and I do not know why it was enlarged. The kidneys showed slight glomerulitis. Perhaps this was a part of the acute infection that the patient had.

Dr. Richardson, will you tell us about the brain?

DR. EDWARD P. RICHARDSON, JR.: The brain was of normal size and weight. The subarachnoid space over the cerebral hemispheres and at the base of the brain contained a thin layer of purulent exudate. On section, an abscess was found in the left occipital lobe, which occupied almost the entire extent of that portion of the brain from the occipital pole to the occipitoparietal junction. The abscess was in free communication with the ventricular system through an opening into the posterior horn of the left lateral ventricle. Microscopical examination showed a cellular reaction in the abscess wall that was consistent with a duration of approximately two weeks.

The reason for the terminal left hemiplegia is not apparent from the pathological findings, but the location of the abscess accounts well for the complete right homonymous hemianopia and the convulsive seizures with right-sided focal aspects. It was situated far enough posteriorly not to involve the motor or somatic sensory regions of the brain, and this explains the fact that the patient had no right hemiparesis or sensory deficit.

A PHYSICIAN: What was the lesion on the forearm?

DR. FENNELL: That was just a small hemangioma.

DR. ALLAN M. BUTLER: Is it odd to you, Dr. Richardson, that this abscess did not result in cells in the spinal fluid?

DR. RICHARDSON: I think that was very strange, particularly since the microscopical sections of the portion of the abscess adjacent to the meninges showed a great many lymphocytes, large mononuclear cells and a few polymorphonuclear leukocytes in the subarachnoid space. One would assume that these cells would have been found in the spinal fluid. I do not have an explanation for their absence.

DR. PHILIP R. DODGE: How often do you see brain abscess and congenital heart disease in the absence of endocarditis?

DR. RICHARDSON: Many such cases have appeared in the literature. Most recently, Clark and Clarke,[3] who reviewed the post-mortem material from the Johns Hopkins Hospital, reported that brain abscess frequently arises in conjunction with cyanotic heart disease without any demonstrable focus of infection elsewhere in the body — specifically, no evidence of bacterial endocarditis. Another excellent article is that of Robbins[4] from the Boston City Hospital in

which he reviewed very thoroughly 3 cases in which the same circumstances occurred. No one knows the exact pathogenesis of these abscesses. It is generally considered that the by-passing of the pulmonary capillary bed must be of importance in the development of these lesions. Robbins points out that it is extremely difficult to produce abscesses in an animal's brain experimentally either by introducing organisms into the blood stream or implanting them directly into the brain. However, abscesses may readily be produced by infection of an area of injury to brain tissue. It is postulated, therefore, that brain abscesses in congenital heart disease with shunts between the pulmonic and systemic circulations may arise in a focus of encephalomalacia resulting from infected paradoxical emboli, or from sterile emboli followed by transient bacteremia. In the previously reported cases, however, and in the present case, it has been impossible to demonstrate either a source of emboli, or that an initial bacteremia occurred. Thus, any theories about pathogenesis are still speculative.

DR. TALBERT: There are two clinical points worthy of emphasis in this case. The first is that one occasionally encounters normal spinal-fluid findings in the presence of brain abscess; therefore, a test deserves repetition before one should be willing to rule out abscess on this basis alone. This does not mean, of course, that the general clinical rule that absence of pleocytosis and increased protein in the spinal fluid is strong evidence against brain abscess is not a useful one. The second point is the common teaching, borne out by this case, that in the presence of congenital heart disease the development of signs of focal brain disease with fever indicates brain abscess until proved otherwise; whereas the development of a similar neurologic picture in rheumatic heart disease is more likely to be indicative of subacute bacterial endocarditis with infected embolization to the brain.

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CASE 39352

PRESENTATION OF CASE

A forty-four-year-old woman was admitted to the hospital because of a mass in the left clavicle.

About six months before admission the patient began to notice pain, stiffness and limitation of abduction in the left shoulder that were thought to be "rheumatic." The removal of several teeth was followed by considerable improvement in the shoulder, but some stiffness still remained. Stiffness had gradually become worse with recurrence of pain and limitation of abduction and elevation. For about four months she had been aware of a lump at the medial end of the left clavicle that had gradually increased in size. On occasions it was tender.

The past history and review of the systems were otherwise noncontributory.

Physical examination showed a well developed and well nourished woman. The examination was not remarkable except for a hard, fusiform, lemon-sized, nontender mass involving the medial end of the left clavicle.

The temperature, pulse, respirations and blood pressure were normal.

The urine was normal. It did not contain Bence-Jones protein. Examination of the blood showed a hemoglobin of 13.6 gm. and a white-cell count of 9100, with 75 per cent neutrophils, 13 per cent lymphocytes, 9 per cent monocytes and 3 per cent eosinophils. The serum total protein was 6.2 gm., the calcium 10.9 mg. the phosphorus 3.1 mg., and the alkaline phosphatase 3.8 units per 100 cc. A roentgenogram of the chest was normal. Examination of the bones revealed almost complete destruction of the sternal end of the left clavicle, the bone in this region being moth eaten and slightly enlarged (Fig. 1). There was also a periosteal reaction. The right side of the fifth cervical vertebra showed similar, less marked changes. The body of the vertebra was not deformed, and there was no soft-tissue thickening. The skull, pelvis, other long bones and the remainder of the spine were normal. A plain film of the abdomen showed normal kidney outlines.

On the second hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. GERALD G. GARCELON*: In summary, we have a forty-four-year-old woman with a mass involving the medial end of the left clavicle that had apparently been noticed four months previously by the patient and had slowly increased in size. There was no history of trauma, and the past history and physical examination, except for the mass, were completely negative. The laboratory findings were all within normal limits. No Bence-Jones protein was found in the urine. The x-ray examinations, however, did show some definite pathologic findings.

May I see the films?

DR. STANLEY M. WYMAN: The chest films show no intrinsic disease in the lungs, heart or mediastinum. The medial end of the left clavicle is destroyed, and on a heavily penetrated film the lesion can be seen expanding the bone and producing some periosteal reaction (Fig. 1). The process is almost entirely destructive. The cervical vertebra described

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in the protocol appears similar, but the involvement is much less severe. The other bones are not remarkable.

DR. GARCELON: From the x-ray findings this patient had what appears to have been a completely osteolytic process involving two bones — the left clavicle and the right side of the body of the fifth cervical vertebra, with no evidence of an osteoblastic process except for slight periosteal reaction in the clavicle. The only other information that is not presented in the protocol and might help in diagnosis before biopsy is a blood Hinton test and tuberculin test. I should only mention syphilis and tuberculosis as rare possibilities. In acquired syphilis, I believe that, with the exception of lesions involving the skull, the bone lesions as a rule are more osteoblastic in nature. Although tuberculosis of the bone does produce chiefly a destructive lesion, it is much more common in children, affecting the bodies of the dorsal vertebras and the ends of the long bones, and, in addition, it is becoming increasingly rare in this country. As a matter of fact, there is no evidence in the protocol to support a diagnosis of any inflammatory lesion of bone such as osteomyelitis. The normal temperature chart, with absence of leukocytosis and acute pain, is certainly not in keeping with the picture of acute osteomyelitis, and the absence of new bone production in the x-ray films does not favor a diagnosis of chronic osteomyelitis.

FIGURE 1. *Roentgenogram of the Left Upper Thorax. Arrows indicate the area of destruction of the medial end of the left clavicle.*

My first consideration in a forty-four-year-old woman with an osteolytic process involving more than one bone is certainly that of metastatic carcinoma with the most likely primary lesion arising in the breast. Other primary lesions as a source of metastases to bone, which must be considered but which are much less common, are those of the thyroid gland, kidney, uterus, cervix, ovary, bladder, stomach and lung. I should certainly expect some evidence of the primary cancer on physical examination, but even in the absence of a palpable lesion in the breast or thyroid gland, I cannot completely exclude the diagnosis of metastatic carcinoma in this case.

My second consideration is multiple myeloma. The age of the patient and the destructive lesions in the clavicle and vertebra are certainly in favor of this diagnosis. The absence of Bence-Jones protein in the urine does not rule out multiple myeloma, since this finding is reported as being positive in about 65 per cent of cases. To support this diagnosis one would like to have an increased total serum protein, an increased serum calcium and, in addition, a sternal puncture showing characteristic plasma cells. The usual case of multiple myeloma undoubtedly presents more than two lesions, which are as a rule smaller than the lesion of the clavicle in this patient and probably more often affect the skull, ribs and pelvis. Even though the characteristic laboratory findings were not present and only two bones were involved in the destructive process, it is difficult to exclude multiple myeloma completely as a possible diagnosis in this case.

The next group of lesions to be considered are the primary neoplasms of bone. In this consideration, one must assume that the process is multiple or that there is a metastasis from one bone to another. I believe that both these assumptions are quite rare although possible. Of the benign bone tumors, the lesions that are more likely to simulate the x-ray findings found in this patient are the benign giant-cell tumors, the chondromas and the eosinophilic granulomas.

Benign giant-cell tumors usually occur in adults and cause destruction of bone with expansion and perforation of the cortex similar to what was seen in this patient's clavicle. However, there is usually no periosteal reaction; the lesion is more frequently asymmetrically located in the epiphysis of the long bones, and almost always trabeculae are present in the destroyed bone until late in the disease. There is some question about whether a giant-cell tumor ever metastasizes as such, and I believe that the general opinion is that a metastasis occurs only after sarcoma has developed in the giant-cell tumor. Since this occurs almost always as a result of inadequate repeated treatment, I do not believe that this patient had a malignant variant of the giant-cell tumor. Benign chondromas may produce central bone destruction with thinning and expanding of the cortex. Cases of multiple bone involvement are reported, but these lesions are usually found in younger patients than the one under discussion. Eosinophilic granuloma produces a central destruction of bone with expansion of the cortex. It is almost always solitary, however, and usually affects the pelvic or skull bones of children or young adults. I believe the lesions are usually small and do not attain the size of the lesion in this patient's clavicle.

Of the primary malignant bone tumors one must certainly consider osteogenic sarcoma. Although these tumors usually occur in the age group of ten to twenty years, they may occur at any age. The common sites are the lower femur, upper tibia and upper humerus, but the clavicle and vertebra may also be affected. The usual x-ray picture is one of central destruction extending through unexpanded cortex and resulting in periosteal reaction. The x-ray picture, however, can be extremely variable and may show destruction with expansion as seen in this patient. I should expect a greater degree of invasion into the soft tissue if this patient had osteogenic sarcoma. Ewing's sarcoma is extremely rare after the age of twenty-five years. The characteristic x-ray picture is one of widening of the shaft caused by stimulation of new bone formation in parallel layers endosteally and subperiosteally raising the periosteum in "onion-peel" fashion. Later in the disease the tumor may produce areas of destruction in the medulla and cortex. The disease frequently metastasizes to other bones. This patient may have had an atypical Ewing sarcoma, but with the information at hand the odds are very much against it.

Diseases of the bone marrow and lymphoid tissue — such as Hodgkin's disease, lymphosarcoma and lymphatic leukemia — occasionally produce change in bones, but there is no apparent characteristic picture by x-ray examination since these may be either osteoblastic or osteoclastic. In the absence of any other manifestations, it seems most unlikely that this patient's bone changes were due to one of these conditions.

After discussing the various possibilities in the differential diagnosis of this patient, I still come back to my first consideration as the most probable diagnosis — that is, metastatic carcinoma. I certainly cannot exclude this diagnosis with the information at hand, and I believe that in a forty-four-year-old woman with more than one bone involved in an osteolytic process, the odds are highly in favor of metastatic carcinoma.

About the source of the metastases, I cannot place the site of the primary lesion since the physical examination was reported as having been negative; however, in a woman of this age, without evidence of a palpable tumor in the breast or thyroid gland and a normal chest film, I should favor hypernephroma as the most likely possibility.

DR. THEODORE L. BADGER: The early history is not entirely accurate in that the patient complained of pain in the joints of the fingers, wrists and shoulders, with discomfort but no redness or swelling of the sternoclavicular joint. No redness of any joints was present, but fusiform swelling of the fingers, particularly the left fourth metatarsal joint, was noted. Otherwise the examination and laboratory studies were noncontributory. This was four months before the admission described in the protocol. The patient was treated with hot soaks and aspirin and thought to have a mild rheumatoid arthritis rather than rheumatic fever. No thought of neoplasm, syphilis or tuberculosis entered the differential diagnosis. She was told to return but did not do so for a little over three months. At that time, two weeks before admission, she was still having multiple joint pains, but there was redness, slight swelling and much tenderness over the left sternoclavicular joint. The joints of the fingers had had a variable amount of pain. X-ray films of the fingers and the left sternoclavicular joint were taken, without suspicion of the lesion described in the left clavicle. No tuberculin test was done.

CLINICAL DIAGNOSIS

Rheumatoid arthritis.
?Myeloma.

DR. GERALD G. GARCELON'S DIAGNOSIS

Metastatic carcinoma to left clavicle and fifth cervical vertebra, ?hypernephroma.

ANATOMICAL DIAGNOSIS

Multiple myeloma.

PATHOLOGICAL DISCUSSION

DR. WINFIELD S. MORGAN: Dr. Taylor, you operated on this patient; will you tell us your findings?

DR. GRANTLEY W. TAYLOR: The operation on this patient was an excision of the left clavicle. A low collar incision was made over the left clavicle, and the platysma was divided. The clavicle was severed near the junction of the middle and outer thirds and the proximal two thirds of the bone were dissected; the muscles were divided away from the bone so as to include any extension of the tumor into the soft parts. After the operation the patient got along very well.

DR. HANELIN: The roentgenogram (Fig. 2) of the resected medial portion of the left clavicle shows extensive bone destruction in association with a

soft-tissue tumor that extends beyond the confines of the bone.

DR. MORGAN: Microscopical sections of the clavicle showed extensive replacement of the bone-marrow portion by sheets of myeloma cells. Cytologically, this case would fall into the intermediate group as defined by Lichtenstein and Jaffe,[1] consisting of cells of varying size and shape some of which were relatively small with stippled nuclei, some of which were somewhat larger, with two or more nuclei and some of which were very large with bizarre hyperchromatic nuclei. One feature common to all the cells was the presence of abundant eosinophilic cytoplasm.

This woman's clinical course was interesting. The excision of the clavicle took place in 1941. Annual roentgenograms of the chest, spine and pelvis during the next three years failed to disclose any new bony lesions. However, in 1945, the skull showed numerous areas of diminished density that had appeared since the last observation. There were similar areas in the ribs, the right and left iliac bones and the neck of the left femur. Several months later she fell while hurrying to catch a train and suffered a mild compression fracture of the ninth dorsal vertebra. Two years later x-ray findings were about the same.

FIGURE 2. *Roentgenogram of Operative Specimen Showing Destruction of the Medial End of the Left Clavicle and the Associated Soft-Tissue Tumor.*

Interestingly enough the patient was well and active during this period. In 1951 she fell while ice-skating and experienced immediate pain in the lower back for which she was admitted to the hospital. At this time the bones of the lumbar spine and pelvis appeared somewhat more osteoporotic than before. There was little change in the lesions in the iliac bones, and no evidence of a new fracture. The urine had a specific gravity of 1.014 and gave a ++ test for albumin; the sediment contained occasional white cells per high-power field. The serum total protein was 6.7 gm., the albumin 4.75 gm., the globulin 1.95 gm. and the nonprotein nitrogen 25 mg. per 100 cc.

In July, 1952, the patient was again admitted to the hospital because of pain in the lower back with radiation down the left leg. The urine gave a +++ test for protein, all of which was Bence-Jones protein. Examination of the blood revealed a hemoglobin of 8.6 gm. per 100 cc. There were no plasma cells in the smear. The patient was given x-ray therapy to the spine and blood transfusions, with only transient improvement. Progressive renal failure necessitating several admissions developed, and she died in uremia four months later.

At autopsy the general body organs were not remarkable except for the kidneys, which weighed only 160 gm. together. Microscopically, they showed the typical features of myeloma kidney in which the distal tubules were distended with large masses of eosinophilic material. The bone-marrow cavities of the spine, right ilium and ribs were replaced by pinkish, jelly-like material, which microscopically had the same appearance as the lesion in the clavicle removed eleven years before.

This case is of interest for several reasons: firstly, a duration of eleven years after removal of the first lesion is unusual and suggests that the presence of multinucleated cells and cells with bizarrely shaped nuclei does not necessarily indicate a rapidly growing lesion; secondly, the total serum protein remained at normal levels throughout the course, and there was never a hyperglobulinemia; thirdly, despite the diffuseness of the bony involvement, no leukemoid element ever developed, and plasma cells were never identified in the smear; fourthly, Bence-Jones protein was found only during the last two years; and finally, there was no evidence of amyloidosis at autopsy, a development that one might reasonably expect in a case of myeloma of this duration.

The relation between the solitary myelomatous tumor and multiple myeloma is still a matter of

dispute in some quarters. This case has demonstrated the development of multiple lesions several years after the diagnosis of a solitary one, and offers support for the view that these two conditions are probably variations of the same disease. The similar cytology of the tumor in the initial lesion and that found at autopsy would be further support for that contention.

DR. BERNARD M. JACOBSON: I first saw this patient six months before she died. At that time the stained blood smear showed no diagnostic abnormalities. The sternal-bone-marrow aspiration revealed 29 per cent of the marrow cells to be members of the plasma cell series, 18 per cent mature plasmacytes and 11 per cent proplasmacytes or "myeloma" cells. A single urine specimen contained a large amount of protein, all of which was Bence-Jones protein. Detection of this protein is not always easy, and it is quite possible that many of the routine laboratory reports of "no Bence-Jones protein present" during the preceding few years were incorrect. Ten days after I first saw the patient, a specimen of serum was taken and by the usual fractionation method showed an albumin content of 4.60 gm. and a globulin content of 1.29 gm. per 100 cc.

In my opinion, one cannot be sure that the initial clavicular lesion eleven years before death represented a so-called solitary myeloma. The absence of other skeletal lesions, the normal hemoglobin content and the normal blood chemical findings together do not rule out multiple myeloma. If a bone-marrow aspiration at that time had been carried out and the marrow found to be normal, I should tentatively accept this case as one of solitary plasmoma. If we assume that this patient had multiple myeloma eleven years before death this case represents a long duration indeed. In his monograph on the clinical and pathological aspects of myeloma, Magnus-Levy[2] cites from the older literature cases of long duration with well established diagnoses of multiple myeloma. His Case 13, ascribed to Groves, lived fourteen years after the known onset of the disease, but this is the only case gathered by Magnus-Levy whose duration exceeded that of the present case. On the other hand, if we assume that this patient's initial lesion consisted of a solitary myeloma we must conclude that dissemination took place at least four years later, when the generalized skeletal lesions were found. This course conforms to that of the vast majority of cases of so-called solitary myeloma. The subject was thoroughly reviewed by Gootnick[3] in 1945. A small proportion of cases may be considered a benign type of tumor, but the vast majority showed dissemination and the clinical evidence of multiple myeloma within a few months or a few years after extirpation of the initial lesion. Unfortunately, most of the cases in the older literature considered to represent solitary plasmoma were not initially studied from the point of view of the bone-marrow histology. In this hospital the incidence of solitary plasmoma is probably not more than 1 in 100 cases of multiple myeloma. It is an exceedingly rare disease.

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HALF-CENTURY OF FLYING — AN EVALUATION

Since December, 1903, when the Wright brothers were able to realize the age-old dream of Icarus at Kitty Hawk, man's conquest of the air space as a medium of transportation and combat has opened up new areas of concern and study for medicine as well as industry. Appropriately enough, during this fiftieth anniversary year of powered flight, a careful evaluation has been made by Ross A. McFarland* of the far-reaching implications of this new mode of transport for the airmen who operate the planes, the ground crews that maintain them, and the public that is borne aloft. His publication is a significant landmark, in that a wide range of information from the various biologic and engineering sciences has been developed and effectively integrated, not only for aviation but for other forms of transportation and for industry in general.

The place of psychologic and medical testing in the selection, education and maintenance of airmen is the first to be treated. A wealth of source material has been reviewed and interpreted for both the professional and the nonprofessional worker. Dr. McFarland amply demonstrates the value of periodic health examinations in selecting applicants and prolonging their useful lives. A study of 232 problem medical cases followed up during a twelve-year period will be of particular interest to physicians. Equal attention is given to the health and safety of ground employees, and the analysis of industrial accidents relates the work of safety engineering and medicine. The important role of the physician in safety programs is clearly defined, a matter of no small importance, since accidents now rank as the major cause of death in younger age groups.

In a section dealing with the maintenance of health and efficiency of airmen, an objective and thorough survey has been made of the influence of exercise, diet, alcohol, tobacco and emotional adjustments on flying safety and prolongation of service; and critical analysis is made of operational fatigue and aging. Much of this information is of practical use to the medical profession.

In a section on sanitation of airports and control of contagious diseases along air routes — which now extend the world over — Dr. McFarland shows how savings can result from an integration of the efforts of entomologists, sanitary experts and other medical specialists. Excellent illustrations are presented, and basic principles are set forth for the control of contagious diseases in the original design of airports, working areas, and aircraft within a diversity of climatic and geographic backgrounds. In addition to animal vectors attention is given to the important possibility of transporting disease by aircraft — since passengers can now be conveyed from an infected area to almost any other part of the world during the incubation period of a major communicable disease. Instances

*McFarland, R. A. *Human Factors in Air Transportation: Occupational health and safety.* 830 pp. New York: McGraw Hill, 1953.

of failure to diagnose such diseases show the importance of the hazards of global air transportation.

No small part of Dr. McFarland's contribution pertains to the care and contentment of passengers, of which the section on transportation of patients is outstanding. The boundaries that should not be exceeded relative to various environmental stimuli in flight are worked out for the design engineer as well as for airline operators and flight surgeons. A review of inflight deaths since 1935 is revealing; less than one such death has occurred among each million revenue passengers using the scheduled airlines. Advantages of air travel for patients are demonstrated — as well as occasional disadvantages. A patient suffering from extreme anoxia or one whose condition may be aggravated by the expansion of trapped gases in the body — from an artificial pneumothorax, for example — should not fly. Basic physiologic and physical principles are set forth that should aid the physician in making decisions regarding his patient's fitness for air travel.

Concluding with an analysis of organization and functions of medical and safety departments in air transportation, Dr. McFarland presents an excellent model for industries other than aviation.

Those who have spent many hours traveling, both by auto and by plane, and have had to cope with medical problems that receive the attention of Dr. McFarland will appreciate the task he has undertaken and carried through to completion so satisfactorily. Readers other than physicians also will have occasion to utilize this treatise as the speeds increase, the ceilings rise, and the powerful jet supplants its propeller-driven predecessor.

REPORT ON GENERAL PRACTICE

Much has been spoken and written about the practice of medicine and "socialized medicine" in recent months, and many charges have been hurled at the conduct of present-day medical practice. Since general practitioners or family physicians comprise two thirds of the total number of doctors in the country, it is refreshing for both physicians and laymen to hear from a qualified representative of this largest group of physicians.

In a recent lay publication* a detailed interview with the president of the American Academy of General Practice appeared. This physician is a general practitioner of twenty-seven years' standing who does his own surgery. He has been a vice-president of the American Medical Association and a member of state and local societies so that he has had a wide experience with medicine as it is practiced today. He has a great array of facts at his command and expresses frank opinions on current medical training and practice. He emphasizes the value of the Academy, with its membership of 16,000, in improving the quality of medical practice by setting up standards of admission and furthering the education of its members. He goes into the matter of selecting a family physician, the emergency-call system now established in most communities, the matter of grievances, fee splitting and so forth. He believes that "ghost surgery" and unnecessary operations are very infrequent. He brings out the fact that more medical students than ever are planning for general practice, that the capacity for training more physicians in medical schools has increased and that the number of young physicians graduating from medical schools is proportionately greater than the population increase.

The writer emphasizes that the distribution of physicians is still poor but that rural districts are trying to make the practice of medicine more attractive to young men. He stresses the long period of training necessary to become a capable physician, as well as the fact that medical schools and not the medical societies determine the admission of students. These and many other items are pointed out in this interview, which should be of interest to both physicians and laymen and should aid greatly in correcting many of the wrong ideas about physicians and medical practice. An abstract of the essential features should be available for still wider distribution.

*U. S. News and World Report, April 3, 1953.

DEAN OF NURSES

It is with a feeling of almost personal pride that the *Journal* records the conferring by Boston University of the degree of Doctor of Humanities on Miss Ruth Sleeper, director of the School of Nursing

and Nursing Service at the Massachusetts General Hospital. The citation marks the quality of her services without enumerating their details — "a distinguished leader in the improvement of education and the use of the services of nurses . . . an exponent and friend of international goodwill . . . you have given nursing graciousness, and by improving its standards you have enhanced the health of many people."

Miss Sleeper's position as director of the nursing school at the Massachusetts General Hospital since 1946, important as it is, is the post around which her larger activities have come to revolve. These have grown with her. A graduate in 1922 of the school that she now directs, she received a B. S. degree from Teachers College, Columbia University, in 1925 and an M. A. in 1935.

She has been chairman of the Education Committee of the International Council of Nurses, a member of the National Commission on Financing of Hospital Care and consultant in nursing at Simmons College. During World War II she served the Division of Nursing Education of the United States Public Health Service as a special consultant, making a survey of nursing in South Carolina.

She has been chairman of the Executive Committee of the International Council of Nurses, a member of a special committee of the Florence Nightingale International Foundation to promote exchange of students, one of the two nurses on the President's Commission for the Health Needs of the Nation and the first president of the National League for Nursing. Last year she was elected to represent American Nursing at the meeting of the World Health Organization in Geneva.

And her spare moments she occupies in writing for nursing journals, pencil sketching and hand-bell ringing!

FOR GREATER EFFICIENCY

Attention is called to a communication from Dr. Mark F. Lesses, chairman of the Committee for the Supervision of the Red Cross Blood Program, published elsewhere in this issue of the *Journal*. In the interest of greater efficiency in the distribution of blood collected under the Massachusetts Red Cross Blood Program, a request is made to all hospitals to submit monthly statements of their needs.

Co-operation in this respect is requested of all blood-bank directors and hospital administrators.

It is estimated that probably one man in every four throughout the human race is, more or less, a smoker of tobacco.

Boston M. & S. J. *August 31, 1853*

MASSACHUSETTS MEDICAL SOCIETY

FRANCIS WINSLOW PALFREY
1876–1953

Dr. Francis W. Palfrey, who died suddenly on June 11, 1953, graduated from Harvard College in 1898 and immediately entered the Harvard Medical School, receiving his degree as doctor of medicine in 1902. He served then as medical house officer at the Massachusetts General Hospital and later at the Children's Hospital in Boston. From 1905 to 1939, he was continuously connected with teaching at Harvard Medical School, becoming assistant professor of medicine in 1929. Three books edited by him, covering the inter-relation of specialties, show his comprehensive medical interests.

As a teacher of clinical medicine at the Boston City Hospital, he practiced the sound methods he had acquired from Shattuck and Fitz, utilizing the five senses to a high degree of accuracy. Only recently, one of his former students narrated his successful accurate localization of chest fluid by percussion when the x-ray film had failed to localize it. Not only was he adept with his ears and fingers, but also his diagnostic reasoning and knowledge of therapy were outstanding.

Like many good teachers he was never attracted by the practice of medicine, and he made no move to acquire either a large consulting practice or to build up a general practice. Not a rich man, he charged ridiculously low fees, but when a patient interested him, he would give much extra time, covering every angle of the case, and to such as these he became the much sought after general practitioner. In particular, sick colleagues sought him out, realizing his ability; to these he became adviser and friend, as well as physician.

Early in World War I, Palfrey went overseas with the British Army to France. With the entrance of the United States into the war, he was placed in charge of medical services at Camp Greene, Charlotte, North Carolina, as Major, M.C., and it was here that he met his future wife, then an Army nurse. His Army career ended after a severe attack of influenzal pneumonia.

Although his Army service was useful, his postwar visit to Poland was more spectacular. Typhus fever was epidemic in many of the armies of Europe. An organism had been found as the probable cause, and the louse was the supposed carrier; delousing was practiced on a large scale by the American and British armies. Soon after the armistice, in 1920, the League of Red Cross Societies decided to send a commission to Poland, then a hot-bed of typhus, and Wolbach, Todd and Palfrey were chosen. They succeeded in proving the causal relation of the rickettsial organism suspected of causing typhus, and made important contributions to its pathology. The published monograph on this work is a model of scientific investigation.

Dr. Palfrey did not come of a long line of family physicians like many of his colleagues in New England. His father was Brigadier General John C. Palfrey in the Civil War; his older brother was studying law, and so he decided to try medicine. He had a good brain, did well in the medical school, and climbed the academic ladder slowly but steadily. He was an accurate and rapid thinker, but slow in expressing his thoughts and conclusions. For this reason his competency was underestimated by the uninitiated. His sister states that, even when he was young, his thinking was invariably "two jumps ahead of his expression." But when at long last he spoke, his choice of words, his meaning and his judgment were accurate. At times, he was inarticulate for long periods. His intimate friends addressed him as the "Wise Old Owl." Although never boisterous and never a long story-teller, he was convivial with friends, and had a strong sense of humor for situations. He was seldom a competitor in sports, with the exception of racing sailing canoes and small "Duxbury Ducks" in the summer with his sons. Probably he derived his chief outdoor satisfaction in his fishing and hunting trips to Cape Cod and the woods of Canada. His enjoyment of the countryside was fully as satisfying to him as success in shooting or fishing. At home, he had few outside interests in spite of excellent manual dexterity, which was unfortunate in his latter days when physical restrictions did not permit expeditions on sea or into the woods.

In his death, we have lost not only a good doctor and an excellent teacher but also, to those who knew him well, a reliable, helpful and generous friend.

J. B. A.

DEATHS

BIRNIE — John M. Birnie, M.D., of East Longmeadow, died on August 8. He was in his seventy-fifth year.

Dr. Birnie received his degree from Harvard Medical School in 1906. He was formerly president of the Massachusetts Medical Society, the Hampden District Medical Society and the New England Surgical Society and was a fellow of the American College of Surgeons and the American Medical Association. He was a member of the staffs of Springfield, Monson State, Wesson Memorial, Mary Lane, Wing Memorial and Noble hospitals.

Dr. Birnie is survived by his widow, two sons, a daughter and two grandchildren.

LALLY — Francis H. Lally, M.D., of Milford, died on August 4. He was in his seventy-ninth year.

Dr. Lally received his degree from Dartmouth Medical School in 1902. He served on the State Board of Health and the Milford Board of Health, and was a fellow of the American Medical Association.

He is survived by his widow and a son.

BOSTON MEDICAL LIBRARY

NONMEDICAL WORKS OF PHYSICIANS

The Library is especially interested in the nonmedical writings of physicians and allied persons, dentists, nurses and so forth, both scientific and nonscientific. In this connection two special gifts are noted.

Dr. Allen G. Rice, of Springfield, who has for some time been collecting the complete nonmedical works of physicians has presented the following sets to the Library:

Oliver Goldsmith. *Miscellaneous Works.* 4 vol. (Paris, 1837.)

J. G. Holland. Timothy Titcomb, Esq., *Works, Poetry and Prose.* 14 vol. (New York, 1885.)

Oliver Wendell Holmes. *Writings.* 14 vol. (Cambridge, 1894–1899.) The Riverside edition, with John T. Morse, Jr. *Life and Letters.* 2 vol. (Cambridge, 1896.)

Charles Lever. *Novels.* 40 vol. (Boston, 1894–1895.) Limited edition, No. 435.

S. Weir Mitchell. *Works.* 16 vol. (New York, 1909.) Author's definitive edition.

Tobias Smollet. *Works.* 12 vol. (New York, 1899–1901.)

Dr. M. R. de Haan, of Grand Rapids, Michigan, conducts a successful *Radio Bible Class*, and his broadcasts are printed in the form of booklets. Dr. de Haan has presented the Library with a collection of 52 of his booklets on scriptural subjects.

PHYSICIAN BOTANIST

Robert John Thornton, 1768?–1837, physician, devoted his life to the writing of botanical and medical books. His output was large, and at the beginning he ruined himself financially by the publication of the lavish *New illustration of the sexual system of Linnaeus*, 1799–1807. This large folio work was first issued in parts, and in 1805 was re-issued as *The Temple of Flora, or garden of nature*. The plates, 31 in number, were re-engraved on a smaller scale than the originals.

The original editions have become scarce and expensive. In a new limited edition (1951) recently published, the plates are reproduced in color and in black-and-white colortype. It is a sumptuous production and is fated to become also a collector's item.

In 1810 in London, Thornton issued his *Botanical extracts: or philosophy of botany*, in three volumes. Also of medical interest are the *New family herbal*, 1810; *Plates of hearts*, 1799; *Facts decisive in favour of the cow-pock*, 1803; *Vaccine vindicia: on the nature of health, with practical observations; and the laws of the nervous and fibrous systems*, 1794-1797; and *The philosophy of medicine*, first published in five volumes in 1796, and going through five editions to 1813. All the works were published in London.

CORRESPONDENCE

SUPERVISION OF BLOOD PROGRAM

To the Editor: The Committee for the Supervision of the Red Cross Blood Program is desirous of ascertaining the total blood needs of hospitals in Massachusetts at regular monthly intervals.

For this purpose, cards will be sent to all hospitals in the State at the end of each month by Dr. Huston J. Banton, who is a member of the Committee and also the medical director of the Massachusetts Red Cross Blood Program.

The Committee would therefore greatly appreciate the cooperation of all blood-bank directors and hospital administrators in the furtherance of this goal.

MARK FALCON LESSES, M.D., *Chairman*

Boston

Committee for the Supervision of the Red Cross Blood Program of the Massachusetts Medical Society

RESTORATION OF LICENSE

To the Editor: At the meeting of the Board of Registration in Medicine held July 16, 1953, the registration of Dr. Kenneth T. Moore, of Hanover, was restored.

ROBERT C. COCHRANE, M.D.
Secretary

State House
Boston

BOOK REVIEWS

Die Nachkommen geisteskranker Elternpaare: Der Einfluss endogener Elternpsychosen auf die Psychosen, Charaktere und Lebensschicksale ihrer Kinder. By Prof. Dr. Med. Günter Elsässer. 8°, cloth, 340 pp., with 38 genealogical tables. Stuttgart: Georg Thieme, 1952. Ganzleinen DM 33. (Distributed by Grune and Stratton, New York.)

The author of this procedurally conservative and clinically well documented monograph is an able member of the noted German school of psychiatric genetics based on the brilliant work of Rüdin and his old-time collaborators in Munich (Brugger, Juda, Kahn, Lange, Luxenburger, Weinberg and so forth) and in recent years carried on by such competent workers as Kranz, Panse and Schulz. In fact, all but 38 of the 134 family units used in the present report (sibships with 2 psychotic parents) came from samples collected by Kahn and Schulz many years ago.

Although highly impressive as a study of rare fertile matings (reproductive despite the presence of "endogenous" types of psychosis in both mates) and subjected to a scrupulously devised system of psychiatric classifications, an analysis of family data of this kind is likely to lose much of its general statistical value because of various methodologic limitations. The given sample required 6 subdivisions, 3 of which (with a total of 61 family units) consisted of matings characterized by an "atypical" psychosis in one or both mates. The remaining parental combinations were formed by 2 schizophrenics (34), 2 manic-depressives (20), and 1 schizophrenic and 1 manic-depressive parent (19).

The psychoses observed in the children of these 6 groups of matings followed strictly the pattern set by their parents and showed a frequency that varied from 30 to 40 per cent. On the whole, the respective rates of psychosis were somewhat lower than those reported by other investigators. However, they were far above the expectancy of persons with only 1 schizophrenic or manic-depressive parent and generally confirmed present genetic theories based on comparative twin studies, especially those on specific gene-controlled predispositions for the two major types of psychosis, schizophrenia and manic-depressive psychosis.

The book supplies a great many interesting data and will be of value to everyone concerned with the complex problems and methods of psychiatric genetics. It provides no final answers, but it demonstrates clearly and forcefully how urgent it is to push on with research in this important field.

FRANZ J. KALLMANN

Handbook of Gynaecological Diagnosis for Practitioners and Students. By Walter Neuweiler, M.D. Translated from the German by Dr. Paul Ederer. 8°, cloth, 448 pp., with 406 illustrations. New York: Grune and Stratton, 1952. $12.00.

This is an admirably idiomatic English translation of a recent German textbook of gynecologic diagnosis by the professor of midwifery and gynecology at the University of Berne. It is concerned solely with methods and technics of diagnosis, and with the systematic description of gynecologic diseases, and does not concern itself at all with the therapeusis and prognosis. It deals systematically with case histories, methods of examination and the standard categories of gynecologic disease. The book is well illustrated with 406 figures in the text, and has an adequate index and a bibliography of 52 titles, of which 32 are German, 10 French and 10 English.

It is a far cry from the days of Moschion, the Greek physician who wrote the first textbook of gynecology in the second century, A.D., but of the many that have appeared since that time, this is certainly one of the best. It will be welcomed and found valuable by both practitioners and students.

ROBERT M. GREEN, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Practical Dermatology for Medical Students and General Practitioners. By George M. Lewis, M.D., professor of clinical medicine (dermatology), Cornell University Medical College, attending dermatologist, New York Hospital, and secretary, American Board of Dermatology and Syphilology. 8°, cloth, 328 pp., with 99 illustrations. Philadelphia: W. B. Saunders Company, 1952. $7.50.

The material in this book is arranged by diseases and covers in concise form the whole field of dermatology. There is a formulary index of drugs and remedies, a bibliography and a comprehensive index. The publishing is excellent.

Surgical Forum: Proceedings of the Forum Session, Thirty-Eighth Clinical Congress of the American College of Surgeons, New York City, September 1952. Surgical Forum Committee, Owen H. Wangensteen, M.D., chairman. 8°, cloth, 716 pp., with illustrations. Philadelphia: W. B. Saunders Company, 1953. $10.00.

A large number of surgeons contributed to this important surgical congress. The papers are divided into sections on the stomach, esophagus and intestine, heart and great vessels, wounds and infection, the heart and blood circulation, gynecology, obstetrics and anesthesia, lungs and liver, shock, portal tension, liver, pancreas and blood coagulation, water balance and electrolytes, plastic surgery and thermal injuries and cancer. There are indexes of authors and subjects, and short lists of references are appended to the papers. The volume should be in all medical libraries and in the collections of surgeons.

Gynecological and Obstetrical Pathology. By Peter A. Herbut, M.D., professor of pathology, Jefferson Medical College of Philadelphia, and director of Clinical Laboratories, Jefferson Medical College Hospital, Philadelphia. 8°, cloth, 683 pp., with 428 illustrations. Philadelphia: Lea and Febiger, 1953. $12.50.

The main part of the book is arranged by organs and on a regional basis. There are chapters on the embryology of the female genital system, physiology and cytology by Dr. Abraham E. Rakoff, and on the Rh factor and blood groups and on the anemias of pregnancy by Dr. L. A. Erf. A comprehensive survey of the pertinent literature is given, and there are extensive bibliographies. The publishing is excellent, and there is a good index. The book should be in all medical libraries and should prove valuable to all gynecologists and obstetricians.

Standard Values in Blood: Being the first fascile of a handbook of biological data. Edited by Errett C. Albritton, M.D., Fry Professor of Physiology, The George Washington University School of Medicine. Prepared under the direction of the Committee on the Handbook of Biological Data, American Institute of Biological Sciences, National Research Council. 4°, paper, 199 pp., with 202 tables. Philadelphia: W. B. Saunders Company, 1952. $4.50.

This technical manual presents in tabular form basic established data on the composition and reactions of the blood. A comprehensive bibliography of 46 pages is appended to the text, and there is a good index. The book is a valuable laboratory and reference tool.

Hamey the Stranger. By John J. Keevil. 8°, cloth, 192 pp., with illustrations. London: Geoffrey Bles, 1952. 21s. net.

This biography tells the story of Baldwin Hamey, a Flemish physician, who went to Russia as court doctor to Czar Fedor in 1594. He remained there until 1597, when he fled to London, where he spent the remainder of his life and where for some time he was forbidden to practice because he was a foreigner. The text is written in narrative form and will be followed by a second book about Hamey's son, who became an eminent London physician.

Diseases of the Chest. By T. Royle Dawber, M.D., senior surgeon, United States Public Health Service, chief of Heart Disease Epidemiology Study, National Heart Institute, and assistant in medicine, Harvard Medical School; and Lloyd E. Hawes, M.D., radiologist, Faulkner Hospital. 4°, cloth, 440 pp., with 216 illustrations. Baltimore: Williams and Wilkins, 1952. $10.00.

This new book is the joint work of an internist and a roentgenologist. The various diseases of the respiratory organs and of the heart are illustrated and discussed in full. A bibliography of selected references is appended to the text, and there is a good index. The combination atlas is recommended for all medical libraries and for physicians interested in the chest and its diseases.

Clinical Applications of Suggestion and Hypnosis. By William T. Heron, professor of psychology, University of Minnesota. Second edition. 12°, cloth, 137 pp. Springfield, Illinois: Charles C Thomas, 1953. $3.75.

The author has added to this new edition of his book a selection of case histories of dental patients in which the use of hypnosis was satisfactory.

Introduction to Physiological Optics. By Armin von Tschermak-Seysenegg, University of Munich, Regensburg Extension. Translation sponsored by the American Committee on Optics and Visual Physiology, of the Section on Ophthalmology, American Medical Association, American Ophthalmological Society and American Academy of Ophthalmology and Otolaryngology. Translated by Paul Boeder, Ph.D., director, Bureau of Visual Science, American Optical Company, and instructor in ophthalmology, Harvard Medical School. 8°, cloth, 299 pp., with 110 illustrations. Springfield, Illinois: Charles C Thomas, 1952. $10.50.

This special textbook was first published in German under the title, *Einführung in die physiologische Optik*, in 1942. This translation makes available to English readers an important volume in which the author discusses his theory of "exact subjectivism." There are indexes of authors and subjects. The book should be in all collections on the eye.

Ophthalmic Pathology: An atlas and textbook. By Jonas S. Friedenwald, Helenor Campbell Wilder, A. Edward Maumenee, T. E. Sanders, John E. L. Keyes, Michael J. Hogan, and W. C. and Ella U. Owens. With the editorial assistance of Helen Knight Steward. Published under the joint sponsorship of the American Academy of Ophthalmology and Otolaryngology and the Armed Forces Institute of Pathology. 4°, cloth, 489 pp., with 240 illustrations. Philadelphia: W. B. Saunders Company, 1952. $18.00.

This atlas of 240 plates also includes the discussion of physiologic mechanisms that influence pathologic change. The first three chapters are devoted to anatomy, physiology, histology and growth and aging. These are followed by chapters on the various pathologic conditions of the eye. Lists of pertinent references are included, and there is a good index. The illustrations are excellent. The volume should be in all collections on the subject.

NONCLINICAL NOTES

GREATER BOSTON CHAPTER OF AMERICAN HEART ASSOCIATION

The following slate of officers was recently elected for the newly formed Greater Boston Chapter of the Massachusetts Heart Association: Dr. Harold D. Levine, president; Dr. Edwin O. Wheeler, vice-president; Dr. Egon E. Kattwinkel, secretary; Mr. Bryant Burkard, chairman of the Board; and Mr. Charles E. Cotting, treasurer.

NOTICES

ANNOUNCEMENTS

Dr. Arthur A. Grant announces the removal of his office from 118 Bailey Street, to McCarthy Clinic, 10 Amesbury Street, Lawrence.

Dr. Vincent P. Perlo announces the opening of an office at 412 Beacon Street, Boston, for the practice of neurology.

Dr. David Kaufman announces the opening of an office for the practice of internal medicine at 851 Beacon Street, Newton Centre.

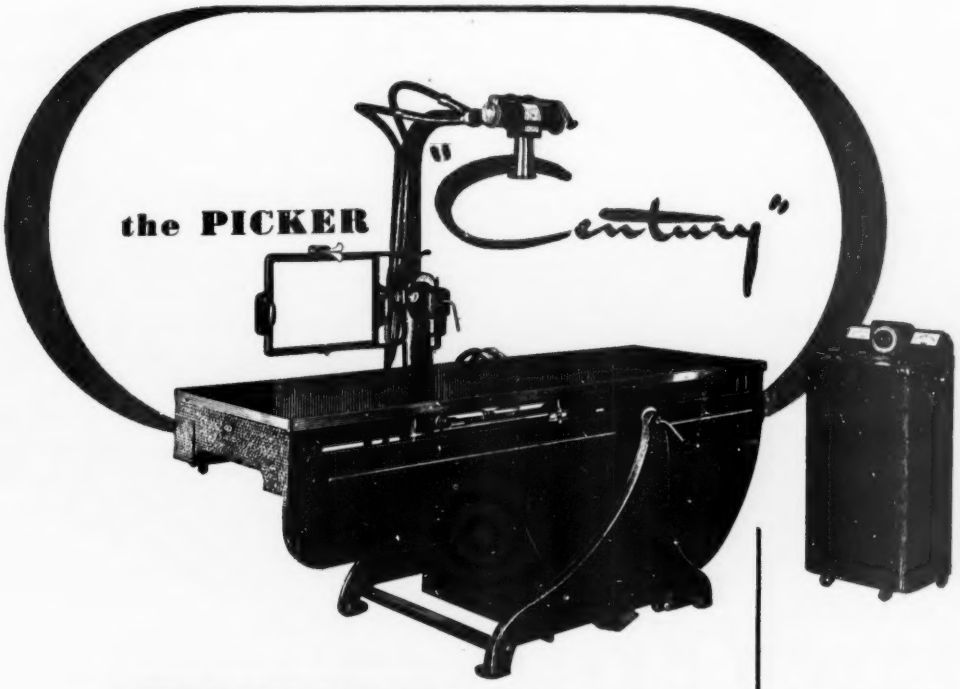
AMERICAN MEDICAL WRITERS' ASSOCIATION

The tenth annual meeting of the American Medical Writers' Association will be held at the Elk's Club, Springfield, Illinois, September 23, during the meeting of the Mississippi Valley Medical Society. Information may be obtained from Harold Swanberg, M.D., Secretary, W. C. U. Building, Quincy, Illinois.

MISSISSIPPI VALLEY MEDICAL SOCIETY

The eighteenth annual meeting of the Mississippi Valley Medical Society will be held at the Elk's Club, Springfield, Illinois, September 23 to 25. Information may be obtained from Harold Swanberg, M.D., Secretary, W. C. U. Building, Quincy, Illinois.

(*Notices concluded on page xiii*)



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NOTICES (*Concluded from page 386*)

SOCIETY MEETINGS AND CONFERENCES

SEPTEMBER 1–28. Consultation Clinic for Crippled Children in Massachusetts. Page 344, issue of August 20.

SEPTEMBER 3–6. Second International Congress on Hippocratic Medicine. Page 302, issue of August 13.

SEPTEMBER 15. South End Medical Club. Page 344, issue of August 20.

SEPTEMBER 23. Middlesex South District Medical Society. Page 260, issue of August 6.

SEPTEMBER 23. American Medical Writers' Association. Page 386.

SEPTEMBER 23–25. Mississippi Valley Medical Society. Page 386.

SEPTEMBER 24–OCTOBER 1. Fourth Congress of Pan American Medical Women's Alliance. Page 124, issue of July 16.

OCTOBER 4–9. American Academy of Pediatrics. Page 1126, issue of June 25.

OCTOBER 5–DECEMBER 21. Hartford Medical Society Program. Page 260, issue of August 6.

OCTOBER 12–14. National Gastroenterological Association. Page 260, issue of August 6.

OCTOBER 12–17. Seventh International Congress of Pediatrics. Page 170, issue of July 23.

OCTOBER 15–17. Annual Course in Postgraduate Gastroenterology. Page 260, issue of August 6.

OCTOBER 17–20. American Association of Blood Banks. Page 1126, issue of June 25.

OCTOBER 19–30. New York Academy of Medicine. Page xvii, issue of June 11.

OCTOBER 25–29. American Institute of Dental Medicine. Page 124, issue of July 16.

OCTOBER 28. New England Obstetrical and Gynecological Society. Page 868, issue of November 27.

NOVEMBER 2–4. New England Postgraduate Assembly. Hotel Statler, Boston.

NOVEMBER 19 and 20. Inter-Society Cytology Council. Page 170, issue of July 23.

DECEMBER 6. American Academy of Dental Medicine. Page 170, issue of July 23.

MAY 31–JUNE 3, 1954. American Urological Association. Page xvii, issue of July 23.

SEPTEMBER 12–15, 1954. Second International Congress of Cardiology. Page 44, issue of July 2.

SEPTEMBER 16–18, 1954. American Heart Association. Annual Scientific Sessions. Page 44, issue of July 2.

DISTRICT MEDICAL SOCIETIES

MIDDLESEX EAST

SEPTEMBER 23.
NOVEMBER 18.
JANUARY 20. (Combined with the Auxiliary.)
MARCH 24.
MAY 12. Annual Meeting. (Harlow Dinner.)

MIDDLESEX SOUTH

SEPTEMBER 23.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, SEPTEMBER 3

THURSDAY, SEPTEMBER 3

*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:00–10:00 a.m. Cardiac Grand Rounds. Main Amphitheater, Children's Medical Center.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

FRIDAY, SEPTEMBER 4

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
*10:00 a.m.–1:00 p.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:30–11:15 a.m. Diabetes Lecture. Dr. Elliott P. Joslin. New England Deaconess Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

SATURDAY, SEPTEMBER 5

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.
*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*11:00 a.m.–12:00 m. Blood Clinic. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, SEPTEMBER 7

*8:00–9:00 a.m. Combined Medical and Surgical Rounds for Diabetic Surgery Cases. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.
12:00 m. Clinicopathological Conference (Boston Floating Hospital). Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*7:00–9:00 p.m. Anesthesia Teaching Conference. Stearns Auditorium, New England Center Hospital.

TUESDAY, SEPTEMBER 8

*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
*12:00 m.–1:00 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.
*12:15–1:15 p.m. X-ray Conference. Dr. Merrill Soaman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Private Dining Room, New England Deaconess Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.

WEDNESDAY, SEPTEMBER 9

*12:00 m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Medical Conference. (Children's Medical Center.) Jimmy Fund Building, 25 Binney Street.
12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. (Children's Medical Center.) Jimmy Fund Building, 25 Binney Street.
*4:00 p.m. Thoracic Conference. Held by Overholt Clinic. Harris Hall, New England Deaconess Hospital.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.

*Open to the medical profession.

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